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# (54) THERMOPHILIC AMINO ACID BIOSYNTHESIS SYSTEM ENZYME GENE OF THERMOTOLERANT CORYNEFORM BACTERIUM

(57) A plurality of primer sets are designed based on a region where conservation at the amino acid level is observed among various microorganisms for known gene sequences corresponding to a gene coding for an enzyme of the L-amino acid biosynthetic pathway derived from *Corynebacterium thermoaminogenes*, preferably an enzyme that functions at a higher temperature compared with that of *Corynebacterium glutamicum*.

PCR is performed by using the primers and chromosomal DNA of *Corynebacterium thermoaminogenes* as a template. The primers with which an amplification fragment has been obtained are used as primers for screening to select a clone containing a target DNA fragment from a plasmid library of chromosomal DNA of *Corynebacterium thermoaminogenes*.

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#### Description

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#### Technical Field

**[0001]** The present invention relates to heat resistant enzyme genes, in particular, genes for enzymes of biosynthetic pathway and uptake system of L-amino acids such as L-glutamic acid, of *Corynebacterium thermoaminogenes*, which is a thermophilic coryneform bacterium.

### Background Art

[0002] The current main stream of the production of L-amino acids such as L-glutamic acid is the fermentative production utilizing coryneform bacteria. As for the fermentative production of L-amino acids, it has been attempted to reduce the cost based on breeding of strains with superior productivity and development of fermentation techniques. Although conventional attempts for realizing the cost reduction were mainly directed to achieving higher yield, energy required for cooling the fermentation heat generated during the culture cannot be ignored in addition to the raw material as the factors concerning the fermentation cost. That is, as for usual microorganisms used for the fermentation, the temperature of the medium rises due to fermentation heat generated by the microorganism themselves during the fermentation, and hence enzymes required for the fermentation may be inactivated or the productive bacteria may be killed. Therefore, it is necessary to cool the medium during the fermentation. Accordingly, in order to reduce the cooling cost, fermentation at high temperatures has been studied for many years. Moreover, if high temperature fermentation becomes possible, the reaction rate may also be improved. However, as for the L-amino acid fermentation, effective high temperature culture has not been realized so far.

[0003] Corynebacterium thermoaminogenes is a bacterium classified into coryneform bacteria like Corynebacterium glutamicum (Brevibacterium lactofermentum), which is commonly used for the fermentation of L-amino acids. However, 30-35°C, and shows the optimum temperature of 37-43°C, which is higher than that of Corynebacterium glutamicum, i.e., to the high temperature region (Japanese Patent Laid-open (Kokai) No. 63-240779/1988).

[0004] Meanwhile, there have been developed techniques for enhancing L-amino acid producing ability of *Coryne-bacterium* and *Brevibacterium* bacteria by introducing a gene coding for an L-amino acid synthesis system enzyme derived from *Escherichia coli* or *Corynebacterium glutamicum* into them. Examples of such an enzyme include; for example, citrate synthase (Japanese Patent Publication (Kokoku) No. 7-121228/1995), which is an enzyme of the L-citrate dehydrogenase, aconitate hydratase (Japanese Patent Laid-open No. 61-268185/1986), iso-cory

[0005] However, any L-amino acid biosynthesis enzymes and genes coding for them derived from thermophilic coryneform bacteria have not been reported.

#### Disclosure of the Invention

[0006] An object of the present invention is to provide genes coding for enzymes derived from *Corynebacterium thermoaminogenes*, preferably enzymes that function at a temperature higher than those of *Corynebacterium glutamicum*.

[0007] The inventors of the present invention extensively studied in order to achieve the aforementioned object. As a result, they successfully isolated genes coding for enzymes of the amino acid biosynthetic pathway of *Corynebacterium thermoaminogenes*, or genes coding for proteins involved in the uptake of amino acids into cells, and thus achieved the present invention.

[0008] That is, the present invention provides the followings.

- (1) A protein having the amino acid sequence of SEQ ID NO: 2 or the amino acid sequence of SEQ ID NO: 2 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, which has isocitrate lyase activity and shows 30% or more of residual activity after a heat treatment at 50°C for 5 minutes.
- (2) A protein having the amino acid sequence of SEQ ID NO: 4 or the amino acid sequence of SEQ ID NO: 4 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, which is involved in acyl Co-A carboxylase activity derived from *Corynebacterium thermoaminogenes*.
- (3) A protein having the amino acid sequence of SEQ ID NO: 6 or the amino-acid sequence of SEQ ID NO: 6 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, which has DtsR activity derived from *Corynebacterium thermoaminogenes*.
- (4) A protein having the amino acid sequence of SEQ ID NO: 8 or the amino acid sequence of SEQ ID NO: 8 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, which has

DtsR activity derived from Corynebacterium thermoaminogenes.

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- (5) A protein having the amino acid sequence of SEQ ID NO: 10 or the amino acid sequence of SEQ ID NO: 10 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, which shows phosphofructokinase activity at 60°C in an equivalent or higher degree compared with the activity at 30°C.
- (6) A protein having the amino acid sequence of SEQ ID NO: 94 or the amino acid sequence of SEQ ID NO: 94 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, which has activity for imparting sucrose assimilating ability to *Corynebacterium thermoaminogenes*.
- (7) A protein having any one of the amino acid sequences of SEQ ID NOS: 17-20 or the amino acid sequence of any one of SEQ ID NOS: 17-20 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, which has a function involved in glutamic acid uptake and derived from *Corynebacterium thermoaminogenes*.
- (8) A protein having the amino acid sequence of SEQ ID NO: 22 or the amino acid sequence of SEQ ID NO: 22 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, which has pyruvate dehydrogenase activity derived from *Corynebacterium thermoaminogenes*.
- (9) A protein having the amino acid sequence of SEQ ID NO: 24 or the amino acid sequence of SEQ ID NO: 24 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, which has pyruvate carboxylase activity derived from *Corynebacterium thermoaminogenes*.
- (10) A protein having the amino acid sequence of SEQ ID NO: 26 or the amino acid sequence of SEQ ID NO: 26 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, which has phosphoenolpyruvate carboxylase activity and shows 50% or more of residual activity after a heat treatment at 45°C for 5 minutes.
- (11) A protein having the amino acid sequence of SEQ ID NO: 28 or the amino acid sequence of SEQ ID NO: 28 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, which has aconitase activity and shows 30% or more of residual activity after a heat treatment at 50°C for 3 minutes.
- (12) A protein having the amino acid sequence of SEQ ID NO: 30 or the amino acid sequence of SEQ ID NO: 30 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, which has isocitrate dehydrogenase activity and shows 50% or more of residual activity after a heat treatment at 45°C for 10 minutes.
- (13) A protein having the amino acid sequence of SEQ ID NO: 32 or the amino acid sequence of SEQ ID NO: 32 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, which has dihydrolipoamide dehydrogenase activity derived from *Corynebacterium thermoaminogenes*.
- (14) A protein having the amino acid sequence of SEQ ID NO: 34 or the amino acid sequence of SEQ ID NO: 34 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, which has 2-oxoglutarate dehydrogenase activity and shows 30% or more of residual activity after a heat treatment at 50°C for 10 minutes.
- (15) A protein having the amino acid sequence of SEQ ID NO: 80 in Sequence Listing or the amino acid sequence of SEQ ID NO: 80 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, which shows glutamate dehydrogenase activity at 42°C in an equivalent or higher degree compared with the activity at 37°C.
- (16) A protein having the amino acid sequence of SEQ ID NO: 90 in Sequence Listing or the amino acid sequence of SEQ ID NO: 90 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, which shows citrate synthase activity at 37°C in an equivalent or higher degree compared with the activity at 23°C.
- (17) A DNA which codes for a protein having the amino acid sequence of SEQ ID NO: 2 or the amino acid sequence of SEQ ID NO: 2 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, and having isocitrate lyase activity.
- (18) The DNA according to (17), which is a DNA defined in the following (a1) or (b1):
  - (a1) a DNA which comprises the nucleotide sequence of SEQ ID NO: 1 in Sequence Listing,
  - (b1) a DNA which is hybridizable with the nucleotide sequence of SEQ ID NO: 1 in Sequence Listing or a primer prepared based on the nucleotide sequence under a stringent condition, and codes for a protein having isocitrate lyase activity.
- (19) A DNA which codes for a protein having the amino acid sequence of SEQ ID NO: 4 or the amino acid sequence of SEQ ID NO: 4 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, and involved in acyl Co-A carboxylase activity.
- (20) The DNA according to (19), which is a DNA defined in the following (a2) or (b2):

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- (a2) a DNA which comprises the nucleotide sequence of SEQ ID NO: 3 in Sequence Listing.
   (b2) a DNA which is hybridizable with the nucleotide sequence of SEQ ID NO: 3 in Sequence Listing or a primer prepared based on the nucleotide sequence under a stringent condition, and codes for a protein involved in acyl Co-A carboxylase activity.
- (21) A DNA which codes for a protein having the amino acid sequence of SEQ ID NO: 6 or the amino acid sequence of SEQ ID NO: 6 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, and having DtsR activity.
- (22) The DNA according to (21), which is a DNA defined in the following (a3) or (b3):
  - (a3) a DNA which comprises the nucleotide sequence of SEQ ID NO: 5 in Sequence Listing.

    (b3) a DNA which is hybridizable with the nucleotide sequence of SEQ ID NO: 5 in Sequence Listing or a
  - primer prepared based on the nucleotide sequence under a stringent condition, and codes for a protein having DtsR activity.
- (23) A DNA which codes for a protein having the amino acid sequence of SEQ ID NO: 8 or the amino acid sequence of SEQ ID NO: 8 including substitution, deletion; insertion, addition or inversion of one or several amino acids residues, and having DtsR activity.
- (24) The DNA according to (23), which is a DNA defined in the following (a4) or (b4):
  - (a4) a DNA which comprises the nucleotide sequence of SEQ ID NO: 7 in Sequence Listing,
  - (b4) a DNA which is hybridizable with the nucleotide sequence of SEQ ID NO: 7 in Sequence Listing or a primer prepared based on the nucleotide sequence under a stringent condition, and codes for a protein having DtsR activity.
- (25) A DNA which codes for a protein having the amino acid sequence of SEQ ID NO: 10 or the amino acid sequence of SEQ ID NO: 10 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, and having phosphofructokinase activity.
- (26) The DNA according to (25), which is a DNA defined in the following (a5) or (b5):
  - (a5) a DNA which comprises the nucleotide sequence of SEQ ID NO: 9 in Sequence Listing.
  - (b5) a DNA which is hybridizable with the nucleotide sequence of SEQ ID NO: 9 in Sequence Listing or a primer prepared based on the nucleotide sequence under a stringent condition, and codes for a protein having phosphofructokinase activity.
- (27) A DNA which codes for a protein having the amino acid sequence of SEQ ID NO: 93 or the amino acid sequence of SEQ ID NO: 93 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, and having invertase activity.
- (28) The DNA according to (27), which is a DNA defined in the following (a6) or (b6):
  - (a6) a DNA which comprises the nucleotide sequence of SEQ ID NO: 93 in Sequence Listing,
  - (b6) a DNA which is hybridizable with the nucleotide sequence of SEQ ID NO: 93 in Sequence Listing or a primer prepared based on the nucleotide sequence under a stringent condition, and codes for a protein having invertase activity.
- (29) A DNA which codes for a protein having any one of the amino acid sequences of SEQ ID NOS: 17-20 or the amino acid sequence of any one of SEQ ID NOS: 17-20 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, and having a function involved in glutamic acid uptake.

  (30) The DNA according to (29), which is a DNA defined in the following (a7) or (b7):
  - (a7) a DNA which comprises the nucleotide sequence of SEQ ID NO: 16 in Sequence Listing,
  - (b7) a DNA which is hybridizable with the nucleotide sequence of SEQ ID NO: 16 in Sequence Listing or a primer prepared based on the nucleotide sequence under a stringent condition, and codes for a protein having a function involved in glutamic acid uptake.
- (31) A DNA which codes for a protein having the amino acid sequence of SEQ ID NO: 22 or the amino acid sequence of SEQ ID NO: 22 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, and having pyruvate dehydrogenase activity.

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- (32) The DNA according to (31), which is a DNA defined in the following (a8) or (b8):
  - (a8) a DNA which comprises the nucleotide sequence of SEQ ID NO: 21 in Sequence Listing.

    (b8) a DNA which is hybridizable with the nucleotide sequence of SEQ ID NO: 21 in Sequence Listing or a
  - primer prepared based on the nucleotide sequence under a stringent condition, and codes for a protein having pyruvate dehydrogenase activity.
- (33) A DNA which codes for a protein having the amino acid sequence of SEQ ID NO: 24 or the amino acid sequence of SEQ ID NO: 24 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, and having pyruvate carboxylase activity.
- (34) A DNA according to (33), which is a DNA defined in the following (a9) or (b9):
  - (a9) a DNA which comprises the nucleotide sequence of SEQ ID NO: 23 in Sequence Listing.
    (b9) a DNA which is hybridizable with the nucleotide sequence of SEQ ID NO: 23 in Sequence Listing or a primer prepared based on the nucleotide sequence under a stringent condition, and codes for a protein having pyruvate carboxylase activity.
- (35) A DNA which codes for a protein having the amino acid sequence of SEQ ID NO: 26 or the amino acid sequence of SEQ ID NO: 26 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, and having phosphoenolpyruvate carboxylase activity.
- (36) The DNA according to (35), which is a DNA defined in the following (a10) or (b10):
  - (a10) a DNA which comprises the nucleotide sequence of SEQ ID NO: 25 in Sequence Listing, (b10) a DNA which is hybridizable with the nucleotide sequence of SEQ ID NO: 25 in Sequence Listing or a primer prepared based on the nucleotide sequence under a stringent condition, and codes for a protein having phosphoenolpyruvate carboxylase activity.
- (37) A DNA which codes for a protein having the amino acid sequence of SEQ ID NO: 28 or the amino acid sequence of SEQ ID NO: 28 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, and having aconitase activity.
- (38) The DNA according to (37), which is a DNA defined in the following (a11) or (b11):
  - (a11) a DNA which comprises the nucleotide sequence of SEQ ID NO: 27 in Sequence Listing, (b11) a DNA which is hybridizable with the nucleotide sequence of SEQ ID NO: 27 in Sequence Listing or as primer prepared based on the nucleotide sequence under a stringent condition, and codes for a protein having aconitase activity.
- (39) A DNA which codes for a protein having the amino acid sequence of SEQ ID NO: 30 or the amino acid sequence of SEQ ID NO: 30 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, and having isocitrate dehydrogenase activity.
  - (40) The DNA according to (39), which is a DNA defined in the following (a12) or (b12):
    - (a12) a DNA which comprises the nucleotide sequence of SEQ ID NO: 27 in Sequence Listing, (b12) a DNA which is hybridizable with the nucleotide sequence of SEQ ID NO: 27 in Sequence Listing or a primer prepared based on the nucleotide sequence under a stringent condition, and codes for a protein having isocitrate dehydrogenase activity.
  - (41) A DNA which codes for a protein having the amino acid sequence of SEQ ID NO: 32 or the amino acid sequence of SEQ ID NO: 32 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, and having dihydrolipoamide dehydrogenase activity.
- (42) The DNA according to (41), which is a DNA defined in the following (a13) or (b13):
  - (a13) a DNA which comprises the nucleotide sequence of SEQ ID NO: 31 in Sequence Listing. (b13) a DNA which is hybridizable with the nucleotide sequence of SEQ ID NO: 31 in Sequence Listing or a primer prepared based on the nucleotide sequence under a stringent condition, and codes for a protein having dihydrolipoamide dehydrogenase activity.
- (43) A DNA which codes for a protein having the amino acid sequence of SEQ ID NO: 34 or the amino acid

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sequence of SEQ ID NO: 34 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, and having 2-oxoglutarate dehydrogenase activity.

- . (44) The DNA according to (43), which is a DNA defined in the following (a14) or (b14):
  - (a14) a DNA which comprises the nucleotide sequence of SEQ ID NO: 33 in Sequence Listing. (b14) a DNA which is hybridizable with the nucleotide sequence of SEQ ID NO: 33 in Sequence Listing or a primer prepared based on the nucleotide sequence under a stringent condition, and codes for a protein having 2-oxoglutarate dehydrogenase activity.
- (45) A DNA which codes for a protein having the amino acid sequence of SEQ ID NO: 80 in Sequence Listing or the amino acid sequence of SEQ ID NO: 80 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, and showing glutamate dehydrogenase activity at 42°C in an equivalent or higher degree compared with the activity at 37°C.
- (46) The DNA according to (45), which is a DNA defined in the following (a15) or (b15):
  - (a15) a DNA which comprises the nucleotide sequence of SEQ ID NO: 79 in Sequence Listing, (b15) a DNA which is hybridizable with the nucleotide sequence of SEQ ID NO: 79 in Sequence Listing or a primer prepared based on the nucleotide sequence under a stringent condition, and codes for a protein showing glutamate dehydrogenase activity at 42°C in an equivalent or higher degree compared with the activity at 37°C.
- (47) A DNA which codes for a protein having the amino acid sequence of SEQ ID NO: 90 in Sequence Listing or the amino acid sequence of SEQ ID NO: 90 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, and showing citrate synthase activity at 37°C in an equivalent or higher degree compared with the activity at 23°C.
- (48) The DNA according to (47), which is a DNA defined in the following (a16) or (b16):
  - (a16) a DNA which comprises the nucleotide sequence of SEQ ID NO: 89 in Sequence Listing, (b16) a DNA which is hybridizable with the nucleotide sequence of SEQ ID NO: 89 in Sequence Listing or a primer prepared based on the nucleotide sequence under a stringent condition, and codes for a protein showing citrate synthase activity at 37°C in an equivalent or higher degree compared with the activity at 23°C.
- (49) A method for producing L-amino acid, which comprises culturing a microorganism introduced with a DNA according to any one of (17) to (48) in a medium to produce and accumulate L-amino acid in the medium, and collecting the L-amino acid from the medium.
- [0009] The term "DNA of the present invention" is used hereinafter for referring to either one or all of the aforementioned DNAs.
- [0010] Hereafter, the present invention will be explained in detail.
- [0011] The nucleotide sequences of the DNA of the present invention, names of the genes, and the proteins encoded by the DNA of the present invention are shown in Table 1.

Table 1

			<del>,</del>
	Nucleotide sequence	Name of gene	Encoded protein (abbreviation)
	SEQ ID NO: 1	aceA	Isocitrate lyase (ICL)
İ	SEQ ID NO: 3	accBC	acyl Co-A carboxylase BC subunit
	SEQ ID NO: 5	dtsR1	DTSR1 protein
	SEQ ID NO: 7	dtsR2	DTSR2 protein
1	SEQ ID NO: 9	pfk	Phosphofructokinase
	SEQ ID NOS:	• •	
	11, 13, 15, 93	scrB	Invertase
	SEQ ID NO: 16	gluABCD	glutamic acid uptake system
	SEQ ID NO: 21	pdhA	pyruvate dehydrogenase
·	SEQTID NO: 23	pc	pyruvate carboxylase
	SEQ ID NO: 25	ррс	phosphoenolpyruvate carboxylase
.,	SEQ ID NO: 27	acn	aconitase

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Table 1 (continued)

Nucleotide sequence	Name of gene	Encoded protein (abbreviation)
•		
	177	isocitrate dehydrogenase
SEQ ID NO: 31	Ipd	dihydrolipoamide dehydrogenase
SEQ ID NO: 33	odhA	2-oxoglutarate dehydrogenase
SEQ ID NO: 79	gdh	glutamate dehydrogenase
SEQ ID NO: 89	gltA	citrate synthase
	SEQ ID NO: 79	SEQ ID NO: 29       icd         SEQ ID NO: 31       Ipd         SEQ ID NO: 33       odhA         SEQ ID NO: 79       gdh

[0012] The open reading frames (ORFs) of SEQ ID NOS: 3, 23, 25, 31 and 33 and the fourth ORF of SEQ ID NO: 16 all start from GTG. Although the amino acids encoded by these GTG are indicated as valine in Sequence Listing, they may be methionine.

[0013] The sequence of SEQ ID NO: 16 contains four ORFs, which correspond to gluA, gluB, gluC and gluD in this order from the 5' end side.

[0014] The aforementioned DNA sequences were isolated from chromosomal DNA of the *Corynebacterium thermoaminogenes* AJ12310 strain (FERM BP-1542). However, the DNA sequences shown in SEQ ID NOS: 11 and 13 were isolated from *Corynebacterium thermoaminogenes* AJ12340 strain (FERM BP-1539) and AJ12309 strain (FERM BP-1541), respectively, which had invertase activity and sucrose assimilating property, because the AJ12310 strain did not have invertase activity and sucrose assimilating property, and the *scrB* gene isolated from the strain had not any open reading frame.

[0015] The Corynebacterium thermoaminogenes AJ12310 strain (also referred to as YS-314 strain) and AJ12309 strain (also referred to as YS-155 strain) were deposited at the National Institute of Bioscience and Human-Technology, Agency of Industrial Science and Technology, Ministry of International Trade and Industry (postal code: 305-8566, 1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki-ken, Japan) on March 13, 1987 and given deposition numbers of FERM P-9246 and FERM P-9245, respectively. Then, they were transferred to international depositions under the provisions of the Budapest Treaty on October 27, 1987, and given deposition numbers of FERM BP-1542 and FERM BP-1541, respectively.

[0016] The AJ12340 strain (also referred to as YS-40 strain) was deposited at the National Institute of Bioscience and Human-Technology, Agency of Industrial Science and Technology, Ministry of International Trade and Industry (postal code: 305-8566, 1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki-ken, Japan) on March 10, 1987 and given a deposition number of FERM P-9277. Then, it was transferred to an international deposition under the provisions of the Budapest Treaty on October 27, 1987, and given a deposition number of FERM BP-1539.

[0017] The nucleotide sequences shown in SEQ ID NOS: 11, 13 and 15 are partial sequences of *scrB*, and the sequences of SEQ ID NOS: 11 and 13 code for partial amino acid sequences of invertase shown in SEQ ID NOS: 12 and 14

[0018] A DNA sequence containing a partial fragment of a target gene can be obtained by comparing already reported nucleotide sequences for the target gene of various microorganisms such as *Brevibacterium lactofermentum* to select a region containing a well-conserved nucleotide sequence, and carrying out PCR using primers designed based on the nucleotide sequence of the region and chromosomal DNA of *Corynebacterium thermoaminogenes* as a template. Further, by performing hybridization using the obtained DNA fragment or a probe prepared based on the sequence of the fragment to screen a chromosomal DNA library of *Corynebacterium thermoaminogenes*, a DNA fragment containing the gene in its full length can be obtained. A DNA fragment containing the gene in its full length can also be obtained by performing genome walking using the obtained partial fragment of the gene. The genome walking can be carried out by using a commercially available kit, for example, TaKaRa LA PCR in vitro Cloning Kit (produced by Takara Shuzo).

[0019] For example, a partial sequence of DNA coding for glutamate dehydrogenase (henceforth the DNA is also referred to as "gdh", and the enzyme is also referred to as "GDH") can be obtained from chromosomal DNA of *Corynebacterium thermoaminogenes* such as the *Corynebacterium thermoaminogenes* AJ12310 strain by PCR (polymerase chain reaction) using the chromosomal DNA as a template and primers having the nucleotide sequences shown in SEQ ID NOS: 77 and 78 of Sequence Listing. Further, by performing genome walking using the obtained partial fragment, the whole *gdh* gene can be obtained.

**[0020]** Further, a partial sequence of DNA coding for citrate synthase (henceforth the DNA is also referred to as "gltA", and the enzyme is also referred to as "CS") can be obtained from chromosomal DNA of Corynebacterium thermoaminogenes such as the Corynebacterium thermoaminogenes AJ12310 strain by PCR (polymerase chain reaction) using the chromosomal DNA as a template and primers having the nucleotide sequences shown in SEQ ID NOS: 83 and 84 of Sequence Listing. Further, by performing genome walking using the obtained partial fragment, the whole gltA gene can be obtained.

[0021] The nucleotide sequences of the aforementioned primers were designed based on a nucleotide sequence in

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a region containing a well-conserved nucleotide sequence among the already reported gdh genes or gltA genes of various microorganisms, which region was found by comparison of the genes:

[0022] As for DNA sequences coding for the other enzymes partial-fragments coding for those enzymes can be similarly obtained by using the primers mentioned in Table 1, and the genes in full length can be obtained by using the

[0023] While the DNA of the present invention was obtained as described above, it can also be obtained from a chromosomal DNA library of Corynebacterium thermoaminogenes by hybridization using an oligonucleotide prepared based on the nucleotide sequences of the DNA of the present invention as a probe

[0024] Methods for preparation of chromosomal DNA, construction of chromosomal DNA library, hybridization, PCR, preparation of plasmid DNA, digestion and ligation of DNA, transformation and so forth are described in Sambrook, J. Fritsch, E.F., Maniatis, T., Molecular Cloning, Cold Spring Harbor Laboratory Press, 1.21 (1989). Further, genome walking can be performed by using a commercially available kit, for example, TaKaRa LA PCR in vitro Cloning Kit (produced by Takara Shuzo).

Specific methods for obtaining the DNA of the present invention will be explained hereafter. [0025]

First, chromosomal DNA of Corynebacterium thermoaminogenes is digested with a suitable restriction enzyme, for example, Sau3Al, and fractionated by agarose gel electrophoresis to obtain a DNA fragment of about 4 to 6 kb. The obtained DNA fragment is inserted into a cloning vector such as pHSG399, and Escherichia coli is transformed with the obtained recombinant plasmid to produce a plasmid library of the chromosomal DNA.

[0027] Separately, primers are produced for use in selecting a clone containing a target gene from a plasmid library by PCR. These primers are designed based on conserved amino acid regions from various microorganisms corresponding to the gene of interest. In the design of primers, a plurality of primer sets are designed considering the codon usage of coryneform bacteria.

[0028] Then, in order to investigate propriety of the produced primers, PCR is performed by using these primers and chromosomal DNA of Corynebacterium thermoaminogenes as a template. Further, PCR is performed by using primers from which an amplification fragment has been obtained as primers for screening and a recombinant plasmid prepared from the plasmid library as a template to select a clone containing the target DNA fragment. This operation can be quickly carried out by performing the PCR for every batch including several tens of transformant strains as primary screening and performing colony PCR for the batch with which an amplification fragment was obtained as secondary screening. The fragment lengths of the amplified genes are shown in Tables 2 to 7.

[0029] If a transformant selected as described above contains a target gene is confirmed by preparing a recombinant DNA from the transformant selected as described above, determining the nucleotide sequence of the inserted fragment by the dideoxy termination method, and comparing the nucleotide sequence with a known gene sequence.

[0030] When the obtained DNA fragment contains a part of the target gene, the deleted part is obtained by genome

[0031] The DNA of the present invention may code for a protein including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, so long as the encoded protein has its original function. The number meant by the term "several" may vary depending on positions in the three-dimensional structure of protein or kinds of amino acid residues. However, in general, such a protein preferably shows homology of 30 to 40% or more, more preferably 55 to 65% or more, with respect to a corresponding whole amino acid sequence of the protein. More specifically, the term "several" means a number of 2 to several hundreds, preferably 2 to several tens, more preferably 2

[0032] Nucleotide and amino acid sequence were analyzed by, for exmaple, the method developed by Lipman and Peason (Science, 227, 1435-1441, 1985) by using commercially available softoware such as Genetyx-Mac computer program (Software Development Co., Tokyo, Japan).

[0033] GDH may be one showing homology of 40 to 80% or more, preferably 80 to 90% or more, for the total amino acid sequence constituting GDH, and showing GDH activity at 42°C equivalent to or higher than the activity at 37°C. In this case, the term "several" means a number of 2 to 30, preferably 2 to 50, more preferably 2 to 10.

[0034] CS may be one showing homology of 40 to 80% or more, preferably 80 to 90% or more, for the total amino acid sequence constituting CS, and showing CS activity at 37°C equivalent to or higher than the activity at 23°C. In this case, the term "several" means a number of 2 to 300, preferably 2 to 50, more preferably 2 to 10.

[0035] A DNA, which codes for the substantially same protein as the original protein as described above, can be obtained by, for example, modifying the nucleotide sequence, for example, by means of the site-directed mutagenesis so that one or more amino acid residues at a specific site should involve substitution, deletion, insertion, addition or inversion. A DNA modified as described above may also be obtained by a conventionally known mutation treatment. The mutation treatment includes a method for treating DNA coding for a target gene in vitro, for example, with hydroxylamine, and a method for treating a microorganism, for example, a bacterium belonging to the genus Escherichia, harboring DNA, coding for the target gene with ultraviolet irradiation or a mutating agent usually used for the mutation treatment such as N-methyl-N'-nitro-N-nitrosoguanidine (NTG) and nitrous acid.

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[0036] The substitution, deletion, insertion, addition, or inversion of nucleotides as described above also includes mutant or variant that naturally occurs due to the difference of strains of *Corynebacterium thermoaminogenes* or the like. [0037] A DNA coding for substantially the same protein as the original protein can be obtained by expressing DNA having a mutation in an appropriate cell, and investigating activity or function of the expressed product protein. The DNA coding for substantially the same protein as the original protein can also be obtained by, for example, isolating a DNA which is hybridizable with a DNA having each of the nucleotide sequences of the sequences of which sequence numbers are mentioned in Table 1 or a coding region thereof, or a probe designed based on the nucleotide sequence under a stringent condition, and which codes for a protein having the activity originally possessed by the protein, from DNA coding for a protein having a mutation or from a cell harboring it. The activity preferably means each enzymatic activity at 42°C for GDH or 37°C for CS.

[0038] The aforementioned probe can be prepared from a DNA having any one of the nucleotide sequences of which sequence numbers are shown in Table 1 or a DNA having any one of the nucleotide sequences by PCR using suitable primers.

**[0039]** The "stringent condition" referred to herein is a condition under which so-called specific hybrid is formed, and non-specific hybrid is not formed. It is difficult to clearly express this condition by using any numerical value. However, for example, the stringent condition includes a condition under which DNAs having high homology, for example, DNAs having homology of not less than 50% are hybridized with each other, and DNAs having homology lower than the above are not hybridized with each other. Alternatively, the stringent condition is exemplified by a condition under which DNAs are hybridized with each other at a salt concentration corresponding to an ordinary condition of washing in Southern hybridization, *i.e.*, 60°C, 1 x SSC, 0.1% SDS, preferably 0.1 x SSC, 0.1% SDS.

[0040] The gene, which is hybridizable under the condition as described above, includes those having a stop codon generated in the gene, and those having no activity due to mutation of active site. However, such genes can be easily removed by ligating the genes with a commercially available activity expression vector, and measuring the activity or function.

[0041] A protein corresponding to each DNA of the present invention can be produced by expressing the DNA in a suitable host-vector system.

[0042] As the host used for the expression of a gene, there can be mentioned various prokaryotic cells including Brevibacterium lactofermentum (Corynebacterium glutamicum), coryneform bacteria such as Corynebacterium thermoaminogenes, Escherichia coli, Bacillus subtilis and so forth, and various eucaryocytic cells including Saccharomyces cerevisiae, animal cells and plant cells. Among these, prokaryotic cells, in particular, coryneform bacteria and Escherichia coli are preferred.

[0043] If the DNA of the present invention is ligated to a vector DNA autonomously replicable in cells of *Escherichia coli* and/or coryneform bacteria and so forth to form a recombinant DNA, and this recombinant DNA is introduced into an *Escherichia coli* cell, the subsequent procedure becomes easy. The vector autonomously replicable in *Escherichia coli* cells is preferably a plasmid vector autonomously replicable in the host cell, and examples thereof include pUC19, pUC18, pBR322, pHSG299, pHSG399, pHSG398, RSF1010 and so forth.

[0044] As the vector autonomously replicable in coryneform bacterium cells, there can be mentioned pAM330 (refer to Japanese Patent Laid-open No. 58-67699/1983), pHM1519 (refer to Japanese Patent Laid-open No. 58-77895/1983) and so forth. Moreover, if a DNA fragment having an ability to make a plasmid autonomously replicable in coryneform bacteria is taken out from these vectors and inserted into the aforementioned vectors for *Escherichia coli*, they can be used as a so-called shuttle vector autonomously replicable in both of *Escherichia coli* and coryneform bacteria.

**[0045]** Examples of such a shuttle vector include those mentioned below. There are also indicated microorganisms that harbor each vector, and accession numbers thereof at international depositories are shown in the parentheses, respectively.

	pAJ655	Escherichia coli AJ11882 (FERM BP-136)
		Corynebacterium glutamicum SR8201 (ATCC39135)
	pAJ1844	Escherichia coli AJ11883 (FERM BP-137)
		Corynebacterium glutamicum SR8202 (ATCC39136)
0	pAJ611	Escherichia coli AJ11884 (FERM BP-138)
	pAJ3148	Corynebacterium glutamicum SR8203 (ATCC39137)
	pAJ440	Bacillus subtilis AJ11901 (FERM BP-140)
	pHC4	Escherichia coli AJ12617 (FERM BP-3532)

[0046] In order to prepare a recombinant DNA by ligating the DNA of the present invention and a vector that functions in coryneform bacteria, the vector is digested with a restriction enzyme that provides an end corresponding to an end of the DNA of the present invention. The ligation is normally attained by using a ligase such as T4 DNA ligase.

[0047] To introduce the recombinant DNA prepared as described above into a host such as coryneform bacteria,

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any known transformation methods that have hitherto been reported can be employed. For instance, employable are a method of treating recipient cells with calcium chloride so as to increase the permeability for DNA, which has been reported for *Escherichia coli* K-12 (Mandel, M. and Higa, A., J. Mol. Biol., 53, 159 (1970)), and a method of preparing competent cells from cells which are at the growth phase followed by introducing the DNA thereinto, which has been reported for *Bacillus subtilis* (Duncan, C.H., Wilson, G.A. and Young, F.E., *Gene*, 1, 153 (1977)). In addition to these, also employable is a method of making DNA-recipient cells into protoplasts or spheroplasts, which can easily take up recombinant DNA, followed by introducing the recombinant DNA into the cells, which is known to be applicable to *Bacillus subtilis*, actinomycetes and yeasts (Chang, S. and Choen, S.N., Molec, Gen. Genet., 168, 111 (1979); Bibb, M.J., Ward, J.M. and Hopwood, O.A., Nature, 274, 398 (1978); Hinnen, A., Hicks, J.B. and Fink, G.R., Proc. Natl. Sci. USA, 75, 1929 (1978)). The transformation of coryneform bacteria can be effectively performed by the electric pulse method (refer to Japanese Patent Laid-open No. 2-207791).

[0048] As for the transformation of thermophilic coryneform bacteria such as Corynebacterium thermoaminogenes, it can be efficiently performed by treating cells with an agent that changes the structure of cell walls of the host cells, and applying an electric pulse to a solution containing DNA and the cells of which structure of the cell walls have been changed. The aforementioned agent is an agent that can change the structure of cell walls so that the cells can uptake the DNA when an electric pulse is applied to a solution containing the cells treated with the agent and the DNA (henceforth also referred to as a "cell wall treatment agent"). Examples of such an agent include agents that inhibit normal synthesis of bacterial cell wall and agents that lyse bacterial cell walls. Specific examples thereof include lysozyme, penicillin G, glycine and so forth.

[0049] Those cell wall treatment agents may be used each alone, or two or more kinds of them may be used in combination. Among the aforementioned agents, lysozyme and penicillin G are preferred, and lysozyme is particularly preferred.

[0050] Furthermore, the transformation of *Corynebacterium thermoaminogenes* can also be performed by applying an electric pulse to a solution containing DNA and the host cells of which cell walls has been weakened by a physical method such as ultrasonication (*FEMS Microbiology Letters*, 151, 135-138 (1987))...

[0051] In order to efficiently express a gene contained in the DNA of the present invention, a promoter that functions in the host cell such as lac, trp and P<sub>L</sub> may be ligated upstream from the coding region of the gene. If a vector containing a promoter is used as the vector ligation of each gene, vector and promoter can be attained by one step.

[0052] The proteins of the present invention, which can be produced as described above, can be purified as required from a cell extract or medium by using usual methods for purifying enzymes such as ion exchange chromatography, gel filtration chromatography, adsorption chromatography, salting out and solvent precipitation.

[0053] It is expected that the proteins of the present invention are excellent in thermal stability or exhibit higher activity at high temperatures compared with the corresponding proteins of *Corynebacterium glutamicum* and so forth. For example, GDH of *Brevibacterium lactofermentum* shows the highest GDH specific activity around 37°C, and the activity is markedly reduced around 42°C. However, GDH of the present invention shows at 42°C the GDH activity equivalent to or higher than the activity at 37°C. In a preferred embodiment, GDH of the present invention shows the highest specific activity around 42°C, and shows the activity even at 45°C.

**[0054]** The GDH activity can be measured by, for example, adding the enzyme to 100 mM Tris-HCl (pH 8.0), 20 mM NH<sub>4</sub>Cl, 10 mM sodium  $\alpha$ -ketoglutarate, 0.25 mM NADPH, and determining change of absorbance at 340 nm (Molecular Microbiology 6, 317-326 (1992)).

[0055] Further, CS of *Brevibacterium lactofermentum* shows the highest CS specific activity around 23°C, and the activity is markedly reduced around 33°C. To the contrary, CS of the present invention shows at 37°C the CS activity equivalent to or higher than the activity at 23°C. In a preferred embodiment, CS of the present invention shows reaction temperature-dependently higher activity up to around 37°C, and shows, even at 40°C, about 40% of the activity with respect to the activity at 37°C.

[0056] The CS activity can be measured by, for example, the method described in Methods in Enzymol., 13, 3-11 (1969).

[0057] Further, other proteins of the present invention typically have the following characteristics. The isocitrate lyase has 30% or more of residual activity after a heat treatment at 50°C for 5 minutes. The phosphofructokinase has, at 60°C, the activity equivalent to or higher than the activity at 30°C. The phosphoenolpyruvate carboxylase has 50% or more of residual activity after a heat treatment at 45°C for 5 minutes. The aconitase has 30% or more of residual activity after a heat treatment at 50°C for 3 minutes. The isocitrate dehydrogenase has 50% or more of residual activity after a heat treatment at 45°C for 10 minutes. The 2-oxoglutarate dehydrogenase has 30% or more of residual activity after a heat treatment at 50°C for 10 minutes.

[0058] The proteins of the present invention can also be obtained from cell extracts of *Corynebacterium thermoaminogenes* such as the *Corynebacterium thermoaminogenes* AJ12310 strain by using each activity as an index and usual purification methods for purifying enzymes such as ion exchange chromatography, gel filtration chromatography, adsorption chromatography, salting out and solvent precipitation.

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[0059] Among the DNA of the present invention, *pfk*, *pdhA*, *pc*, *ppc*, *acn*, *icd*, *gdh* and *gltA* (names of the enzymes encoded by these are shown in Table 1) can be introduced into L-amino acid production bacteria such as coryneform bacteria to enhance their L-amino acid producing ability. It is also expected that coryneform bacteria introduced with the DNA of the present invention become possible to produce L-amino acid at a temperature higher than usual. The L-amino acid includes L-glutamic acid, L-aspartic acid, L-lysine, L-arginine, L-proline, L-glutamine and so forth.

**[0060]** For example, it is expected that L-glutamic acid production bacteria such as coryneform bacteria introduced with the *gdh* gene or *gltA* gene come to be able to produce L-glutamic acid at a temperature higher than usual. Further, although CS of *Brevibacterium lactofermentum* may not fully function at a usual culture temperature, for example, 31.5°C, the activity can be enhanced by introducing the *gltA* gene of the present invention.

[0061] Further, dtsR1 and dtsR2 are genes that code for proteins imparting resistance to surfactant to coryneform bacteria (DTSR protein), and coryneform L-glutamic acid producing bacteria of which these genes are disrupted produce a marked amount of L-glutamic acid even under a condition where biotin is present in such an amount that a wild strain becomes to be substantially unable to produce L-glutamic acid. Further, if dtsR1 and dtsR2 genes of coryneform L-glutamic acid producing bacteria having L-lysine producing ability are amplified, the bacteria are imparted with an ability to produce a marked amount of L-lysine (WO95/23224, Japanese Patent Laid-open (Kokai) No. 10-234371/1998).

**[0062]** The *scrB* gene can be used for improvement of coryneform bacteria for use in the production of L-amino acids by using coryneform bacteria in a medium containing sucrose.

[0063] By deleting aceA, accBC, Ipd or odhA of L-glutamic acid producing coryneform bacteria and so forth, their L-glutamic acid productivity can be enhanced. Further, gluABCD is a gene cluster of the L-glutamic acid uptake system, and by deleting one to four of gluA, gluB, gluC and gluD in coryneform L-glutamic acid producing bacteria, the amount of L-glutamic acid accumulated in the medium can be increased. aceA, accBC, lpd, odhA and gluABCD of the present invention can be used for disruption of these genes on chromosome.

[0064] The medium used for producing L-amino acids by utilizing a microorganism introduced with the DNA of the present invention may be a usual medium that contains a carbon source, a nitrogen source, inorganic ions and other organic trace nutrients as required. As the carbon source, there can be used hydrocarbons such as glucose, lactose, galactose, fructose, sucrose, blackstrap molasses and starch hydrolysate; alcohols such as ethanol and inositol; or organic acids such as acetic acid, fumaric acid, citric acid and succinic acid.

[0065] As the nitrogen source, there can be used inorganic ammonium salts such as ammonium sulfate, ammonium nitrate, ammonium chloride, ammonium phosphate and ammonium acetate, ammonia, organic nitrogen such as peptone, meat extract, yeast extract, corn steep liquor and soybean hydrolysate, ammonia gas; aqueous ammonia and so forth.

[0066] As the inorganic ions (or sources thereof), added is a small amount of potassium phosphate, magnesium sulfate, iron ions, manganese ions and so forth. As for the organic trace nutrients, it is desirable to add required subtracts such as vitamin B<sub>1</sub>, yeast extract and so forth in a suitable amount as required.

[0067] The culture is preferably performed under an aerobic condition attained by shaking, stirring for aeration of the like for 16 to 72 hours. The culture temperature is controlled to be at 30°C to 47°C, and pH is controlled to be 5 to 9 during the culture. As for the culture temperature, the culture may be performed at a temperature suitable for culture of a microorganism not introduced with the DNA of the present invention or a temperature higher than that. For adjustment of pH, inorganic or organic acidic or alkaline substances, ammonia gas and so forth can be used.

[0068] Collection of L-amino acids from fermentation broth can be attained by a combination of known methods such as techniques utilizing ion exchange resin, precipitation, crystallization and so forth depending on the kind of the L-amino acids.

## Brief Explanation of the Drawings

[0069] Fig. 1 shows variation with temperature in activity of glutamate dehydrogenases derived from the *Coryne-bacterium thermoaminogenes* AJ12310 strain and the *Brevibacterium lactofermentum* 2256 strain.

[0070] Fig. 2 shows thermal stability of glutamate dehydrogenases derived from the AJ12310 strain and the 2256 strain.

[0071] Fig. 3 shows variation with temperature in activity of citrate synthases derived from the AJ12310 strain and the 2256 strain.

[0072] Fig. 4 shows thermal stability of citrate synthases derived from the AJ12310 strain and the 2256 strain.

[0073] Fig. 5 shows variation with temperature in activity of isocitrate lyases derived from the AJ12310 strain and the 2256 strain.

[0074] Fig. 6 shows thermal stability of isocitrate lyases derived from the AJ12310 strain and the 2256 strain.

[0075] Fig. 7 shows variation with temperature in activity of phosphofructokinases derived from the AJ12310 strain and the 2256 strain.

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[0076] Fig. 8 shows thermal stability of phosphofructokinases derived from the AJ12310 strain and the 2256 strain [0077] Fig. 9 shows variation with temperature in activity of phosphoenolpyruvate carboxylases derived from the AJ12310 strain and the 2256 strain.

[0078] Fig. 10 shows thermal stability of phosphoenolpyruvate carboxylases derived from the AJ12310 strain and the 2256 strain.

[0079] Fig. 11 shows variation with temperature in activity of aconitases derived from the AJ12310 strain and the 2256 strain.

[0080] Fig. 12/shows thermal stability of aconitases derived from the AJ12310 strain and the 2256 strain.

[0081] Fig. 13 shows variation with temperature in activity of isocitrate dehydrogenases derived from the AJ12310 strain and the 2256 strain.

[0082] Fig. 14 shows thermal stability of isocitrate dehydrogenases derived from the AJ12310 strain and the 2256 strain.

[0083] Fig. 15 shows thermal stability of 2-oxoglutarate dehydrogenases derived from the AJ12310 strain and the 2256 strain.

[0084] Fig. 16 shows construction of plasmid pSCR155 carrying scrB gene.

[0085] Fig. 17 shows construction of plasmid pPDHA-2 carrying pdhA gene.

[0086] Fig. 18 shows L-glutamic acid productivity of a pdhA gene-amplified strain: (a) 37°C and (b) 44°C.

[0087] Fig. 19 shows is construction of a plasmid pICD-4 carrying icd gene.

[0088] Fig. 20 shows L-glutamic acid productivity of an icd gene-amplified strain: (a) 37°C and (b) 44°C.

[0089] Fig. 21 shows construction of plasmids pHSG299YGDH and pYGDH.

[0090] Fig. 22 shows construction of plasmids pHSG299YCS and pYCS.

# Best Mode for Carrying out the Invention

[0091] Hereafter, the present invention will be further specifically explained with reference to the following examples.

# Example 1

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<1> Production of plasmid library of Corynebacterium thermoaminogenes

[0092] The Corynebacterium thermoaminogenes AJ12310 strain was cultured in CM2B liquid medium (1 g/dl of yeast extract (produced by Difco), 1 g/dl of polypeptone (produced by Nippon Seiyaku), 0.5 g/dl of NaCl, 10 μg/dl of biotin, pH 7.0 (adjusted with KOH)) at 37°C for 15 hours, and its chromosomal DNA was prepared from the 10 ml of the medium by using a chromosomal DNA extraction kit (Bacterial Genome DNA Purification Kit (produced by Advanced Genetic Technologies)). The obtained DNA was partially digested with a restriction enzyme Sau3Al, and subjected to 0.8% agarose gel electrophoresis to fractionate the DNA. Then, a band corresponding to a DNA fragment of about 4 to 6 kb was excised from the gel, and a DNA fragment of the objective size was obtained by using a DNA gel extraction kit (GIBCO BRL, Concert™ Rapid Gel Extraction System).

[0093] The plasmid pHSG399 (produced by Takara Shuzo) was fully digested with *Bam*HI, and its end was dephosphorylated by using alkaline phosphatase (CIAP; produced by Takara Shuzo). This vector fragment and the aforementioned chromosomal DNA fragment were ligated by using a DNA ligation kit produced by Takara Shuzo, and *Escherichia coli* JM109 was the transformed with the obtained recombinant vector. Selection of transformants was performed on LB agar medium (containing 1.5 g/dl of agar) containing 30 μg/ml of chloramphenicol, 0.04 mg/ml of IPTG (isopropyl-β-D-thiogalactopyranoside) and 0.04 mg/ml of X-Gal (5-bromo-4-chloro-3-indolyl-β-D-galactoside) to obtain about 4000 white colonies.

<2> Design of primers for amplification of each gene

[0094] Primers for use in selection of a clone containing each target gene by PCR from the plasmid library obtained above were designed. The target genes were mentioned above.

[0095] The primers were designed based on a known gene sequence of coryneform bacteria, *i.e.*, its sequence of a region where conservation at the amino acid level was observed when compared with corresponding genes of other microorganisms. Considering the codon usage of coryneform bacteria, a plurality of primer sets were designed for each gene.

[0096] To examine propriety of the prepared primers, PCR was performed by using these primers and chromosomal DNA of the *Corynebacterium thermoaminogenes* AJ12310 strain as a template to amplify each gene fragment. As a result, when the PCR was performed by using the primers shown in the upper rows of Tables 2 to 7 under the conditions indicated as "PCR conditions for obtaining partial fragment" in the tables, an amplified fragment was observed for all

of the genes. The parenthesized numbers after the primer sequences indicate the sequence numbers in Sequence Listing. These primers were used as primers for screening mentioned below.

50 55	35 40 45	20 25 30	5 10
	Ë	Paklo 3	
Gene	aceA	accBC	dtsR1
5'→3'Primer	CCTCTACCCAGCGAACTCCG (35)	ACGGCT (37)	ACGGCCCAGCCCTGACCGAC (39)
3'→5'Primer	CTGCCTTGAACTCACGGTTC (36)	CGGTGACTGGGTGTTCCACC (38)	AGCAGCGCCATGACGGCGA (40)
PCR conditions for		94°C, 5 min	94°C, 5 min
obtaining partial			
fragment and PCR	, 2 sec	98°C, 5 sec	98°C, 5 sec
conditions for	66°C, 2 sec, 30 cycles	66°C, 2 sec, 30 cycles	66°C, 2 sec, 30 cycles
screening	Z-Taq	2-Taq	Z-Tag
Conditions	of 94°C, 7 min	94°C, 7 min	94°C, 7 min
colony PCR	•		
	91°C, 30 sec	91°C, 30 sec	91°C, 30 sec
,	55°C, 1 sec	55°C, 1 sec	55°C, 1 sec
	72°C, 2.5 min, 30 cycles	72°C, 2.5 min, 30 cycles	72°C, 2.5 min, 30 cycles
	Ex-Tag	Ex-Taq	Ex-Tag
Amplified fragment	824bp	673bp	805bp

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Gene	dtsR2	pfk	ar ca
5'→3'Primer	ACGGCCCAGCCCTGACCGAC (41) CGTCATCCGAGGAATCGTCC (43) GGNCGHYTBAAYGAYCC	CGTCATCCGAGGAATCGTCC (43)	GGNCGHYTBAAYGAYCC
3'→5'Primer	AGCAGCCCCATGACGGCGA (42)	CGTGGCGGCCCATGACCTCC (44)	ر
PCR conditions for 94	94°C, 5 min	94°C, 5 min	94°C, 5 min
obtaining partial			
fragment and PCR	98°C, 5 sec	98°C, 5 sec	98°C, 5 sec
conditions for	66°C, 2 sec, 30 cycles	66°C, 2 sec, 30 cycles	50°C, 10 sec
screening	Z-Tag	2-Tag	72°C, 20 sec, 40 cycles
			Z-Taq
			•
Conditions of	94°C, 7 min	94°C 7 min	94°C, 7 min
colony PCR			,
	91°C, 30 sec	91°C 30 sec	91°C, 30 sec
	55°C, 1 sec	55°C 1 sec	55°C, 1 sec
	72°C, 2.5 min, 30 cycles	72°C 2.5 min 30 cycles	72°C, 2.5 min, 30 cycles
	Ex-Tag	Ex-Tag	Ex-Tag
Amplified fragment	805bp	472bp	500bp

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Table 4

···5	Gene	gluABCD	pdhA
5	5'→3'Primer	CCATCCGGATCCGGCAAGTC (47)	ACTGTGTCCATGGGTCTTGGCCC (49)
	3'→5'Primer	AATCCCATCTCGTGGGTAAC (48)	CGCTGGAATCCGAACATCGA (50)
	PCR	94°C, 5 min	94°C, 5 min
10	conditions		
	for obtaining	98°C, 5 sec	98°C, 5 sec
	partial	50°C, 10 sec	50°C, 10 sec
	fragment	72°C, 20 sec, 30 cycles	72°C, 20 sec, 30 cycles
15		Z-Taq	Z-Taq
	Amplified	500bp	1200bp
	fragment		
	Conditions	94°C, 5 min	94°C, 5 min
20	for screening		
	PCR and	94°C, 30 sec	94°C, 30 sec
16	colony PCR		50°C, 1 min
1			72°C, 2 min, 30 cycles
25		EX-Taq	EX-Taq

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Table 5

	Table 5	·
Gene	pc	ррс
5'→3'Primer	GGCGCAACCTACGACGTTGCAATGCG (51)	GGTTCCTGGATTGGTGGAGA (5
3'→5'Primer	TGGCCGCCTGGGATCTCGTG (52)	CCGCCATCCTTGTTGGAATC (5
PCR	94°C, 5 min	94°C 5 min
conditions		
for	98°C, 5 sec	98°C 5 sec
obtaining	55°C, 80 sec 30 cycles	50°C 5 sec
partial	Z-Taq	72°C 10 sec 30 cycles
fragment		Z-Taq
Amplified	781bp	1000bp
fragment		
Conditions	94°C, 5 min	94°C, 5 min
for		
screening	98°C, 5 sec	98°C, 5 sec
PCR	55°C, 80 sec 30 cycles	50°C, 5 sec
	Z-Taq	72°C, 10 sec, 30 cycl
		Z-Taq
Conditions	94°C, 5 min, 1 cycles	94°C, 5 min
for colony		
PCR	98°C, 5 sec	98°C, 5 sec
	55°C, 80 sec, 50 cycles	50°C, 10 sec
	Z-Taq	72°C, 20 sec, 50 cycl
		Z-Tag

						<del></del>	<del></del>	<del></del>	<del></del>		· . ·	
			(59)	5								
10		pal	TTC (	7	8	72°C, 20 sec	500bp	94°C, 5 min	94°C, 30 sec 57°C, 1 min	72°C, 1 min, 30 cycles Ex-Taq	TACGAGGAGCAGATCCTCAA (63) TTGACGCCGGTGTTCTCCAG	(64)
20 25 30	Hoh I de		GACATTTCACTCGCTGGACG (57)	1	Š		1500bp	Same as above				ì
35 40 45		acn	GTIGGIACIGAYTCSCATAC (55) GCIGGAGAIATGTGRTCIGT (56)	94°C, 1 min	96°C, 20 sec	C, 2	1500bp	Same as above				
50		Gene	5'→3'Primer 3'→5'Primer	PCR conditions	for obtaining	fragment	Amplified fragment	Conditions for screening	PCR and colony PCR	Screening PCR	5'→3'Primer 3'→5'Primer	

5 10 15	Lnd	G(67) S1:ATCATCGCAACCGGTTC (69) (68) S2:TACGAGGAGCAGATCCTCAA(70)		HindIII	94°C, 1 min	94°C, 30 sec 57°C, 2 min	72°C, 1 min, 30 cycles LA-Tag	
7able 6 (Cont.)	icd	65) S1:CCGTACTCTCAGCCTTCTG(67) S1:ATCATCGCAACCGGTTC (66) S2:TCGTCCTTGTTCCACATC (68) S2:TACGAGGAGCAGATCCT	S1:TCCGATGTCATCATCGAC (73) S2:ATGTGGAACAAGGACGAC (74)	Sall(N') PstI(C')	94°C, 1 min	30 sec 2 min	72°C, 2.5 min, 30 cycles LA-Taq	
35 40 45	acn	S1:GGTGAAGCTAAGTTAGC 65) S2:AGCTACTAAACCTGCACC (66)	S1:GAACCAGGAACTAGCTTCACC(71) S2:GAACCAGGAACTATTGAACC(72)	PstI(N') HindIII(C')	N' 94°C, 1 min		72°C, 2 min, 30 cycles LA-Tag C' 94°C, 1 min	30
50	Gene	LA cloning (N') 3'→5'Primer	LA Cloning (C') 5'→3'Primer	Restrictione enzyme	Conditions for LA	cloning		

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NSDOCID: <EP\_\_\_1219712A1\_I\_>

### EP 1.219 712 A15 \* 28

# Table 7

Gene	odhA
5'→3'Primer	ACACCGTGGTCGCCTCAACG (61)
3'→5'Primer	TGCTAACCCGTCCCACCTGG (62)
PCR conditions	94°C, 5 min
for obtaining	
partial fragment	98°C, 5 sec
	66°C, 2 sec, 30 cycles
	Z-Taq
	<u> </u>
Amplified	1306bp
fragment	
LA cloning (N')	S1:GTACATATTGTCGTTAGAACGCGTAATACGACTCA(75)
5'→3'Primer	S2:CGTTAGAACGCGTAATACGACTCACTATAGGGAGA(76)
Restriction	XbaI
Conditions for	First time 94°C, 30 sec
LA cloning	55°C, 2 min
	72°C, 1 min 30 cycles
v.	LA-Taq
	Second time 94°C, 1 min
	98°C, 20 sec
	68°C, 15 min, 30 cycles
	72°C 10 min
	LA-Taq

<3> Screening of plasmid library by PCR

[0097] A clone containing a target gene was selected from the plasmid library by PCR. Sixty colonies were picked up from each plasmid library, and replicated onto two LB agar medium plates. The 60 colonies of each plate were combined, inoculated to a test tube containing 4 ml of LB liquid medium and cultured for 15 hours. Then, a plasmid mixture was respectively obtained by using a plasmid DNA extraction kit produced by Promega. By using this plasmid mixture as a template and primers for screening prepared for each target gene, PCR was performed with the conditions shown as "conditions for screening PCR" in each table to select a clone from which a DNA fragment of the same size as that obtained by PCR using chromosomal DNA as a template had been amplified.

[0098] The nucleotide sequence of the amplified DNA fragment was determined by using a Big Dye dye terminator cycle sequencing kit produced by Perkin-Elmer, and investigating its homology to known gene information to determine if the target gene was obtained or not.

[0099] As for *lpd*, since any DNA fragment was not amplified with the primers produced in <2>, other primers for screening were prepared based on the determined nucleotide sequence.

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<4> Selection of clone harboring target gene by colony PCR

[0100] By using a plate that was an origin of a plasmid mixture for which amplification of the target gene fragment was confirmed, colony PCR was performed to select a clone containing the gene fragment. The colony PCR was performed with the conditions shown in Tables 2-7.

[0101] Plasmid DNA was collected from a selected transformant and the nucleotide sequence of the inserted DNA fragment was determined. When the full length of the target gene was not inserted in the inserted DNA fragment, and a upstream region, downstream region or the both were deleted, primers were prepared based on the determined nucleotide sequence, with which a gene fragment comprising the nucleotide sequence of the target gene in its full length was obtained by using TaKaRa LA PCR in vitro Cloning Kit (Takara Shuzo). Then, its nucleotide sequence was determined.

[0102] The outline of LA PCR cloning was as follows. Two kinds of primers each having one of the nucleotide sequences of two regions of the inserted DNA fragment were produced. Chromosomal DNA of Corynebacterium thermoaminogenes AJ12310 strain was digested with various restriction enzymes, and ligated to a cassette primer corresponding to each of the restriction enzymes. By using this as a template, PCR was performed with a primer (S1) corresponding to a position distant from the deletion region and a cassette primer (C1) corresponding to a position outside the cassette primer among the prepared primers. Then, another PCR was performed with a primer (S2) corresponding to a position near the deletion region and a cassette primer (C2) corresponding to a position inside the cassette primer among the prepared primers. In this way, a DNA fragment containing the deleted region was obtained. By ligating the obtained DNA fragment with the already obtained DNA fragment, a DNA fragment containing the target gene in full length could be obtained. Since 5' end of the cassette did not have a phosphate group, a nick was formed at the ligation site of the 3' end of the DNA fragment and the 5' end of the cassette. Therefore, the DNA synthesis from the primer C1 stopped at this ligation site in the first PCR, and thus non-specific amplification did not occur. Therefore, specific amplification could be attained.

[0103] The primers and the reaction conditions used for the LA PCR cloning are shown in Tables 2-7. In the tables, the primers mentioned with "(N')" are primers used for the cloning of an upstream deleted portion, and the primers mentioned with "(C')" are primers used for the cloning of a downstream deleted portion. PCR was performed twice according to the instruction attached to the LA PCR cloning kit. Among the primers mentioned in the tables, the primers (S1) used for the first reaction are shown in the upper row, and the primers (S2) used for the second reaction are shown in the lower row.

[0104] The nucleotide sequences of the DNA fragments containing each gene obtained as described above were determined in the same manner as mentioned above. Those nucleotide sequences and amino acid sequences that can be encoded by those nucleotide sequences are shown in SEQ ID NOS: 1-34. The sequences shown with the sequence numbers are summarized in Explanation of Sequence Listing mentioned hereinafter.

[0105] As for scrB, any open reading frame was not found. Since the Corynebacterium thermoaminogenes AJ12310strain did not have the invertase activity and did not have sucrose assimilating property, an scrB gene fragment was obtained in a similar manner from Corynebacterium thermoaminogenes AJ12340 and AJ12309 strains having the sucrose assimilating property. As a result, a DNA fragment having an open reading frame was obtained from the both

#### Example 2: Acquisition of gdh and gltA gene

<1> Investigation of GDH activity of Corynebacterium thermoaminogenes

45 [0106] Cells of a wild strain of Corynebacterium thermoaminogenes, the AJ12310 strain, was grown on CM-2B agar medium (1 g/dl of yeast extract (produced by Difco), 1 g/dl of polypeptone (produced by Nippon Seiyaku), 0.5 g/dl of NaCl, 10 μg/dl of biotin, 1.5 g/dl of agar, adjusted to pH 7.0 with KOH). The cells were inoculated to a 500-ml volume flask containing 20 ml of a medium for flask having the following composition and cultured at 37°C for 17 hours (until the residual sugar reached about 1 g/dl).

50 [0107] Similarly, cells of the 2256 strain (ATCC13869) of Brevibacterium lactofermentum grown on CM-2B agar medium were cultured at 31.5°C for 17 hours.

[Medium for flask]

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Glucose		3 g/dl

(continued)

KH <sub>2</sub> PO <sub>4</sub>	0.1 g/dl
MgSO <sub>4</sub> ·H <sub>2</sub> O	0.04 g/di
FeSO <sub>4</sub> ·7H <sub>2</sub> O	1 mg/dl
MnSO <sub>4</sub> ·4H <sub>2</sub> O	1 mg/dl
Vitamin B <sub>1</sub> -HCl	200 μg/L
Biotin	50 μg/L
(NH <sub>4</sub> ) <sub>2</sub> SO <sub>4</sub>	1.5 g/dl
Soybean protein hydrolysis solution	48 mg/dl
(Memeno (T-N))	
CaCO <sub>3</sub> (Official regent)	5 g/dl
(separately sterilized)	
pH 8.0 (adjusted with KOH)	

**[0109]** About 1 ml of the above culture medium was centrifuged at 1000 rpm for 1 minute to remove  $CaCO_3$ , and the cells were washed twice with 200 mM K-phosphate buffer (pH 6.9) and suspended in 300  $\mu$ l of the same buffer. The obtained cell suspension was sonicated for 5 minutes to disrupt the cells, centrifuged at 1000 rpm for 30 minutes to obtain a crude enzyme solution as the supernatant.

[0110] The optimum reaction temperature and the thermal stability of GDH activity were investigated using the aforementioned crude enzyme solution. The measurement of GDH activity was performed by adding the crude enzyme solution to a reaction mixture (100 mM Tris-HCl (pH 8.0), 20 mM NH $_4$ Cl, 10 mM sodium  $\alpha$ -ketoglutarate, 0.25 mM NADPH) and measuring change of absorbance at 340 nm. The protein concentration of the crude enzyme solution was quantified by the Bradford method (Bio-Rad Protein Assay Kit was used) using bovine serum albumin as the standard through measurement of absorbance at 595 nm. The absorbance was measured by using HITACHI U-2000 (produced by Hitachi).

[0111] The GDH activity measured at various reaction temperatures is shown in Fig. 1. While the ATCC13869 strain showed the highest specific activity of GDH around 37°C and the activity markedly decreased around 42°C, the AJ12310 strain showed the highest specific activity around 42°C and it showed the activity even at 45°C.

[0112] Then, the thermal stability of GDH was investigated. The crude enzyme solution was left at 65°C for 0 to 30 minutes before the reaction, and then the enzyme activity was measured at 30°C. The results are shown in Fig. 2. As clearly seen from the results, while GDH of the ATCC13869 strain was inactivated by the heat treatment for 5 minutes, GDH of the AJ12310 strain maintained the activity even after the heat treatment for 30 minutes. In addition, the crude enzyme solution of the AJ12310 strain showed substantially no change in the GDH activity even after the heat treatment at 65°C for 90 minutes (data are not shown).

<2> Examination of CS activity of Corynebacterium thermoaminogenes

[0113] The optimum reaction temperature and thermal stability of CS were investigated by using crude enzyme solutions prepared from the cells of the *Corynebacterium thermoaminogenes* AJ12310 strain and the *Brevibacterium tactofermentum* ATCC13869 strain in the same manner as in Example 1. The measurement of CS activity was performed by adding each crude enzyme solution to a reaction mixture (100 mM Tris-HCl (pH 8.0), 0.1 mM DTNB (5,5'-dithiobis-(2-nitrobenzoic acid)), 200 mM sodium L-glutamate, 0.3 mM acetyl CoA), and measuring change of the absorbance at 412 nm.

[0114] The CS activity measured at various reaction temperatures is shown in Fig. 3. The ATCC13869 strain showed the highest specific activity of CS around 23°C and the activity markedly decreased around 33°C. However, the AJ12310 strain showed high specific activity in a reaction temperature-dependent manner up to around 37°C and it showed the activity even at 40°C in a degree corresponding to about 40% of the activity at 37°C.

[0115] Then, thermal stability of CS was investigated. The crude enzyme solution was left at 33-55°C for 5 minutes before the reaction, and then the enzyme activity was measured at 30°C. The results are shown in Fig. 4. Whereas CS of the ATCC13869 strain was inactivated by the heat treatment at 35-40°C, CS of the AJ12310 strain maintained about 40% of the activity even after the heat treatment at 50°C.

<3> Acquisition of gdh gene of Corynebacterium thermoaminogenes

[0116] The already reported nucleotide sequences of gdh gene of various microorganisms were compared. A region

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in which nucleotide sequences were well conserved was selected, and primers having the nucleotide sequences shown in SEQ ID NOS: 77 and 78 were prepared based on the nucleotide sequence of the region.

[0117] PCR was performed by using chromosomal DNA prepared from the *Corynebacterium thermoaminogenes* AJ12310 strain using Bacterial Genome DNA Purification Kit (produced by Advanced Genetic Technologies) as a template and the aforementioned primers. Based on the obtained DNA fragment, genome walking was performed by using TaKaRa LA PCR in vitro Cloning Kit (produced by Takara Shuzo) to obtain the whole *gdh* gene, of which whole nucleotide sequence was determined. The result is shown in SEQ ID NO: 79. Further, the amino acid sequence deduced from this nucleotide sequence is shown in SEQ ID NO: 80.

[0118] The *gdh* gene of the *Brevibacterium lactofermentum* ATCC13869 strain was obtained in a similar manner, and its nucleotide sequence was determined. The result is shown in SEQ ID NO: 81. The amino acid sequence encoded by this nucleotide sequence is shown in SEQ ID NO: 82.

[0119] Homology was investigated for the nucleotide sequences of the *gdh* gene and the amino acid sequences of GDH of the *Corynebacterium thermoaminogenes* AJ12310 strain and the *Brevibacterium lactofermentum* ATCC13869 strain determined as described above, and the known *gdh* gene and amino acid sequence of GDH of the *Corynebacterium glutamicum* (*C. glutamicum*) ATCC13032 strain (Molecular Microbiology 6, 317-326 (1992)). The results are shown in Table 8 (for nucleotide sequences) and Table 9 (for amino acid sequences).

Table 8:

•		•	
Homology of r	nucleotide seque	ences of various	gdh genes
	ATCC13869	ATCC13032	AJ12310
ATCC13869	·	94.5%	82.4%
ATCC13032			78.1%
AJ12310	-	:	-

Table 9

Homology of amino acid sequences of various GDH			
	ATCC13869	ATCC13032	AJ12310
ATCC13869	-	90.8%	91.7%
ATCC13032	-	·	83.4%
AJ12310	-	-	.1=

<4> Acquisition of altA gene of Corynebacterium thermoaminogenes

**[0120]** The already reported nucleotide sequences of *gltA* gene of various microorganisms were compared. A region in which nucleotide sequences were well conserved was selected, and primers having the nucleotide sequences shown in SEQ ID NOS: 83 and 84 were prepared based on the nucleotide sequence of the region.

[0121] PCR was performed by using chromosomal DNA prepared from the *Corynebacterium thermoaminogenes* AJ12310 strain (FERM BP-1542) using Bacterial Genome DNA Purification Kit (produced by Advanced Genetic Technologies) as a template and the aforementioned primers 7 and 8, and the nucleotide sequence of the amplified nucleotide sequence of about 0.9 kb was determined.

[0122] On the basis of the obtained nucleotide sequence of *gltA* gene of *Corynebacterium glutamicum* (Microbiol., 140, 1817-1828 (1994)), the primers of SEQ ID NOS: 85, 86, 87 and 88 were prepared. PCR was performed in a manner similar to the above by using chromosomal DNA of AJ12310 as a template and the primers of SEQ ID NOS: 85, 86, 87 and 88, and the nucleotide sequence of the amplified DNA fragment was specified to determine the whole nucleotide sequence of the *gltA* gene. The result is shown in SEQ ID NO: 89. Further, an amino acid sequence expected from this nucleotide sequence is shown in SEQ ID NO: 90.

[0123] The gltA gene of the Brevibacterium lactofermentum 2256 strain was obtained in a similar manner, and its nucleotide sequence was determined. The result is shown in SEQ ID NO: 91. The amino acid sequence encoded by this nucleotide sequence is shown in SEQ ID NO: 92.

[0124] Homology was investigated for the nucleotide sequences of the *gltA* gene and the amino acid sequences of CS of the *Corynebacterium thermoaminogenes* AJ12310 strain and the *Brevibacterium lactolermentum* ATCC13032 strain determined as described above, and the known *gltA* gene and amino acid sequence of CS of the *Corynebacterium* 

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glutamicum ATCC13032 strain (*Microbiol.*: 140, 1817-1828 (1994)): The results are shown in Table 10 (for nucleotide sequences) and Table 11 (for amino acid sequences).

### Table 10:

Homology of r	nucleotide seque	ences of various	gltA genes
	ATCC13869	ATCC13032	AJ12310
ATCC13869	-	99.5%	85.7%
ATCC13032	-		85.6%
AJ12310	. · · · · ·		-

#### Table 11

Homology	of amino acid se	equences of vari	ous CS
	ATCC13869	ATCC13032	AJ12310
ATCC13869	-	99.3%	92.1%
ATCC13032	-		92.1%
AJ12310	<u>-</u>	-	-

# Example 3: Acquisition of scrB gene of Corynebacterium thermoaminogenes

[0125] Since an *scrB* gene fragment was obtained from the *Corynebacterium thermoaminogenes* AJ12309 strain as shown in Example 1, it was attempted to obtain the total sequence of the gene. First, a partial fragment was obtained in the same manner as in Example 1 using the primers shown in SEQ ID NO: 45 and SEQ ID NO: 46. These primers were synthesized based on the *scrB* sequence of the *Brevibacterium lactofermentum* 2256 strain (Japanese Patent Laid-open No. 08-196280/1996).

[0126] Separately, chromosomal DNA was prepared from the AJ12309 strain by using Bacterial Genome DNA Purification Kit (Advanced Genetic Technologies Corp.). Sterilized water was added to 0.5 μg of this chromosomal DNA, 50 pmol each of the aforementioned primers, 4 μl of dNTP mixture (2.5 mM each), 5 μl of 10 x Z-Taq Buffer (Takara Shuzo) and 2 U of Z-Taq (Takara Shuzo) to prepare a PCR reaction mixture in a total volume of 50 μl. PCR was performed with a cycle of denaturation at 98°C for 5 seconds, association at 50°C for 10 seconds and extension reaction at 72°C for 20 seconds, which was repeated for 30 cycles, by using the above reaction mixture and a thermal cycler GeneAmp PCR System 9600 (PE) to amplify a partial fragment of *scrB* of about 600 bp.

[0127] Then, the total sequence of *scrB* was determined by using an LA PCR in vitro Cloning Kit (Takara Shuzo). All of the procedure was performed in accordance with the protocol attached to the LA PCR in vitro Cloning Kit. Based on the obtained partial sequence, primers shown in SEQ ID NOS: 97, 98, 99 and 100 were synthesized. For the first PCR reaction for sequencing an upstream region, the primers shown in SEQ ID NOS: 95 and 97 and chromosomal DNA of AJ12309 strain digested with *Eco*T14I as a template DNA were used. For the second PCR reaction, the primers shown in SEQ ID NOS: 96 and 98 were used. For the first PCR reaction for sequencing a downstream region, the primers shown in SEQ ID NOS: 95 and 99 and chromosomal DNA of AJ12309 strain digested with *Sal*I (Takara Shuzo) as a template DNA were used. For the second PCR reaction, the primers shown in SEQ ID NOS: 96 and 100 were used. By the above procedure, a sequence of a full length of 1656 bp containing ORF of *scrB* was determined. This nucleotide sequence is shown in SEQ ID NO: 93, and a deduced amino acid sequence is shown in SEQ ID NO: 94.

Example 4: Examination of thermal stability of isocitrate lyase, phosphofructokinase, phosphoenolpyruvate carboxylase, aconitase, isocitrate dehydrogenase and 2-oxoglutarate dehydrogenase

[0128] Thermal stability was investigated for the following enzymes derived from *Corynebacterium thermoaminogenes*. In this Example, protein concentrations were measured by the Bradford method (Bio-Rad Protein Assay Kitwas used) using bovine serum albumin as a standard protein. Further, measurement of absorbance was performed by using HITACHI U-2000 (Hitachi) unless otherwise indicated.

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<1> Isocitrate lyase .

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[0129] Thermal stability of activity of isocitrate lyase (henceforth also referred to as "ICL") derived from the *Coryne-bacterium thermoaminogenes* AJ12310 strain and ICL derived from the *Brevibacterium lactofermentum* 2256 strain (ATCC13869) was investigated. For the activity measurement, used were cells of which culture in a medium having the composition mentioned in Table 2 was terminated before all of the carbon source was completely consumed. The method of the activity measurement was one described in Dieter J. Reinscheid *et al.*, *J. Bacteriol.*, *176* (12), 3474 (1994). Specifically, the cells were washed with 50 mM Tris buffer (pH 7.3), suspended in the same buffer, and disrupted by sonication (INSONATOR 201M produced by KUBOTA was used, 200 W, 5 minutes). After the sonication, the suspension was centrifuged (13000 x g, 30 minutes) to remove undisrupted cells to prepare a crude enzyme solution.

[0130] The crude enzyme solution was added to a reaction system containing 50 mM MOPS-NaOH (pH 7.3), 5 mM dithiothreitol, 15 mM MgCl<sub>2</sub>, 1 mM EDTA, 5 mM D-threo-isocitrate, 0.2 mM NADH and 18 U of LDH (lactate dehydrogenase), and absorbance at 340 nm at various temperatures (30, 40, 50, 60 or 70°C) was measured by a Hitachi spectrophotometer U-3210. The measurement results for various reaction temperatures were shown in Fig. 5. Further, the crude enzyme solution was pretreated at 50°C (pretreatment time: 5 minutes or ,15 minutes), and the activity was measured at 37°C. The results are shown in Fig. 6.

[0131] As a result, ICL of the AJ12310 strain showed the maximum activity at 60°C, whereas ICL of the 2256 strain showed the maximum activity around 50°C. Further, while ICL of the 2256 strain was completely inactivated after the pretreatment for 5 minutes, ICL of the AJ12310 strain maintained half of the activity after the pretreatment for 5 minutes. Thus, the stability of ICL of the AJ12310 strain at high temperatures was confirmed.

Table 12

Composition of medium for ICL activity measurement		
Component	Concentration	
(NH <sub>4</sub> ) <sub>2</sub> SO <sub>4</sub>	5 g/l	
Urea	5 g/l	
KH <sub>2</sub> PO₄	0.5 g/l	
K₂HPO₄	0.5 g/l	
MOPS	20.9 g/l	
MgSO <sub>4</sub> ·7H <sub>2</sub> O	0.25 g/l	
CaCl <sub>2</sub> ·7H <sub>2</sub> O	10 mM	
CuSO <sub>4</sub> ·7H <sub>2</sub> O	0.2 mg/l	
Biotin	. 0.2 mg/l	
MnSO <sub>4:</sub> 7H <sub>2</sub> O	10 mg/l	
FeSO <sub>4</sub> ·7H <sub>2</sub> O	10 mg/l	
ZnSO <sub>4</sub> ⋅7H <sub>2</sub> O	1 mg/l	
Acetic acid	4%	

<2> Phosphofructokinase

[0132] Thermal stability of activity of phosphofructokinase (henceforth also referred to as "PKF") derived from the *Corynebacterium thermoaminogenes* AJ12310 strain and PKF derived from the *Brevibacterium lactofermentum* 2256 strain was investigated. For the activity measurement, used were cells of which culture in a medium having the composition mentioned in Table 13 was terminated before all of the saccharide was completely consumed. The method of the activity measurement was one described in Michiko Mori *et al.*, *Agric. Biol. Chem.*, *51* (10), 2671 (1994). Specifically, the cells were washed with 0.1 M Tris buffer (pH 7.5), suspended in the same buffer, and disrupted by sonication (INSONATOR 201M produced by KUBOTA was used, 200 W, 5 minutes). After the sonication, the suspension was centrifuged (13000 x q, 30 minutes) to remove undisrupted cells to obtain a crude enzyme solution.

**[0133]** The crude enzyme solution was added to a reaction system containing 100 mM Tris buffer (pH 7.5), 0.2 mM NADH, 10 mM MgCl $_2$ , 2 mM NH $_4$ Cl, 10 mM KCl, 0.2 mM phosphoenolpyruvic acid, 6.4 mM fructose-6-phosphate, 1 mM ATP and 40  $\mu$ g of LDH/PK (pyruvate kinase), and absorbance at 340 nm was measured at various temperatures

(30, 40, 50; 60 or 70°C) by a Hitachi spectrophotometer U-3210. The measurement results for various reaction temperatures were shown in Fig. 7. Further, the crude enzyme solution was pretreated at 50°C (pretreatment time: 1, 3, 5 or 10 minutes), and the activity was measured at 37°C. The results are shown in Fig. 8.

[0134] As a result, PKF of the AJ12310 strain showed the maximum activity around 50°C, whereas PKF of the 2256 strain showed the maximum activity around 30°C. Thus, it was confirmed that the optimum temperature of PKF of the AJ12310 strain resided in a high temperature region.

Table 13

Composition of medium for F	PFK activity measurement	
, Component Concentration		
Polypeptone `	20 g/l	
Yeast extract	20 g/l	
Sodium chloride	5.g/l	
Glucose	20 g/l	

#### <3> Phosphoenolpyruvate carboxylase

[0135] Thermal stability of activity of phosphoenolpyruvate carboxylase (henceforth also referred to as "PEPC") derived from the *Corynebacterium thermoaminogenes* AJ12310 strain and PEPC of the *Brevibacterium lactofermentum* 2256 strain was examined.

[0136] Cells of the AJ12310 strain grown on CM-2B agar medium were inoculated to a 500-ml volume flask containing 20 ml of a medium for flask (8 g/dl of Glucose, 0.1 g/dl of  $KH_2PO_4$ , 0.04 g/dl of  $MgSO_4 \cdot H_2O$ , 1 mg/dl of  $FeSO_4 \cdot TH_2O$ , 5 mg/dl of  $MnSO_4 \cdot 4H_2O$ , 3 g/dl of  $NH_4 \cdot 2SO_4$ , 48 mg/dl of TN (soybean protein hydrolysis solution), 200  $\mu$ g/L of vitamin B<sub>1</sub>, 300  $\mu$ g/L of biotin, 50  $\mu$ l/l of GD-113 (antifoaming agent), 5 g/dl of CaCO<sub>3</sub> (Official regent, separately sterilized); pH 8.0 (adjusted with KOH)), and cultured at 37°C. Cells of the 2256 strain grown on CM-2B agar medium were similarly cultured at 31.5°C.

[0137] The above culture broth in which the cells were grown to the logarithmic growth phase was centrifuged at 1000 rpm for 1 minute to remove CaCO<sub>3</sub>, and the cells were washed 3 times with washing buffer (100 mM Tris/HCl pH 8.0, 10 mM MgSO<sub>4</sub>, 1 mM DTT 20% glycerol) sonicated to disrupt the cells, and centrifuged at 15 krpm for 10 minutes to remove cell debris. The supernatant was further centrifuged at 60 krpm for 1 hour to obtain a crude enzyme solution as the supernatant.

[0138] By using the above crude enzyme solution, optimum reaction temperature and thermal stability of the PEPC activity were investigated. The measurement of PEPC activity was performed by adding the crude enzyme solution to a reaction mixture (100 mM Tris/H<sub>2</sub>SO<sub>4</sub> (pH 8.5), 5 mM phosphoenolpyruvic acid, 10 mM KHCO<sub>3</sub>, 0.1 mM acetyl-CoA, 0.15 mM NADH, 10 mM MgSO<sub>4</sub>, 10 U of malate dehydrogenase, 0.1 mM DTT), and measuring change of the absorbance at 340 nm in 800 µl of reaction volume.

[0139] The PEPC activity measured at various reaction temperatures is shown in Fig. 9. While the activity of the 2256 strain markedly decreased at 40°C, the AJ12310 strain showed substantially no decrease of the activity even at 40°C.

[0140] Then, the thermal stability of PEPC was investigated. The crude enzyme solution was left at 45°C for 0-20 minutes before the reaction, and then the enzyme activity was measured at 20°C. The results are shown in Fig. 10. As clearly seen from the results, whereas the PEPC activity of the 2256 strain was substantially lost after the heat treatment for 10 minutes, PEPC of the AJ12310 strain maintained the activity even after the heat treatment for 20 minutes.

[0141] These results demonstrated the stability of PEPC of the AJ12310 strain at a high temperature.

### <4> Aconitase

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**[0142]** Aconitase (henceforth also referred to as "ACN") derived from the *Corynebacterium thermoaminogenes* AJ12310 strain and ACN derived from the *Brevibacterium lactofermentum* 2256 strain were measured, and thermal stability thereof was examined.

[0143] Cells of the AJ12310 strain grown on CM-2B agar medium were inoculated to a 500-ml volume flask containing 20 ml of a medium for flask having the same composition as mentioned in <3>, and cultured at 37°C. Cells of the 2256 strain grown on CM-2B agar medium were similarly cultured at 31.5°C.

[0144] The above culture broth in which the cells were grown to the logarithmic growth phase was centrifuged at

1000 rpm for 1 minute to remove CaCO<sub>3</sub>, and the cells were washed 3 times with 50 mM Tris/HCl pH 7.5. sonicated to disrupt the cells, and centrifuged at 15 krpm for 10 minutes to obtain a crude enzyme solution as the supernatant. [0145] By using the above crude enzyme solution, optimum reaction temperature and thermal stability of ACN activity were investigated. The measurement of ACN activity was performed by adding the crude enzyme solution to a reaction mixture (20 mM Tris/HCl (pH7.5), 50 mM NaCl, 20 mM isocitrate 3Na), and measuring change of the absorbance at 240 nm in 800 µl of reaction volume.

[0146] The ACN activity measured at various reaction temperatures is shown in Fig. 11. The AJ12310 strain showed higher activity at a higher temperature compared with the 2256 strain.

[0147] Then, the thermal stability of ACN was investigated. The crude enzyme solution was left at 50°C for 0-15 minutes before the reaction, and then the enzyme activity was measured at 30°C. The results are shown in Fig. 12. As clearly seen from the results, ACN of the AJ12310 strain showed less activity decrease due to the heat treatment compared with ACN of the 2256 strain.

[0148] These results demonstrated the stability of ACN of the AJ12310 strain at a high temperature.

15 <5> Isocitrate dehydrogenase

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[0149] Thermal stability of activity of isocitrate dehydrogenase (henceforth also referred to as "ICDH") derived from the *Corynebacterium thermoaminogenes* AJ12310 strain and ICDH derived from the *Brevibacterium lactofermentum* 2256 strain was examined.

[0150] Cells of the AJ12310 strain grown on CM-2B agar medium were inoculated to a 500-ml volume flask containing 20 ml of a medium for flask having the same composition as mentioned in <3>, and cultured at 37°C. Cells of the 2256 strain grown on CM-2B agar medium were similarly cultured at 31.5°C.

[0151] The above culture broth in which the cells were grown to the logarithmic growth phase was centrifuged at 1000 rpm for 1 minute to remove CaCO<sub>3</sub>, and the cells were washed 3 times with 50 mM Tris/HCl pH 7.5, sonicated to disrupt the cells, and centrifuged at 15 krpm for 10 minutes to obtain a crude enzyme solution as the supernatant.

**[0152]** By using the above crude enzyme solution, optimum reaction temperature and thermal stability of ICDH activity were investigated. The measurement of ICDH activity was performed by adding the crude enzyme solution to a reaction mixture (35 mM Tris/HCl, 0.35 mM EDTA (pH 7.5), 1.5 mM MnSO<sub>4</sub>, 0.1 mM NADP, 1.3 mM isocitrate 3Na), and measuring change of the absorbance at 340 nm in 800 µl of reaction volume.

[0153] The ICDH activity measured at various reaction temperatures is shown in Fig. 13. While the activity of the 2256 strain markedly decreased at 70°C, substantially no activity decrease was observed even at 70°C for the AJ12310 strain.

[0154] Then, the thermal stability of ICDH was investigated. The crude enzyme solution was left at 45°C for 0-15 minutes before the reaction, and then the enzyme activity was measured at 30°C. The results are shown in Fig. 14. As clearly seen from the results, while only about 15% of residual activity was observed after the heat treatment for 15 minutes for the 2256 strain, about 60% of residual ICDH activity was observed for the AJ12310 strain.

[0155] These results demonstrated the stability of ICDH of the AJ12310 strain at a high temperature.

<6> 2-Oxoglutarate dehydrogenase

[0156] 2-Oxoglutarate dehydrogenase (henceforth also referred to as "ODHC") derived from the *Corynebacterium thermoaminogenes* AJ12310 strain and ODHC derived from the *Brevibacterium lactofermentum* 2256 strain were measured, and thermal stability thereof was examined.

[0157] For the activity measurement, used were cells of which culture in a medium having the composition mentioned in Table 14 was terminated before all of the saccharide was completely consumed. The method of the activity measurement was one described in Isamu Shiio et al., Agric. Biol. Chem., 44 (8), 1897 (1980). Specifically, the cells were washed with 0.2% potassium chloride, suspended in 100 mM TES-NaOH (pH 7.5), 30% glycerol solution, and disrupted by sonication (INSONATOR 201M produced by KUBOTA was used, 200 W, 5 minutes). After the disruption by sonication, the suspension was centrifuged (13000 x g, 30 minutes) to remove undisrupted cells, and subjected to gel filtration using the same buffer and Sephadex-G25 to prepare a crude enzyme solution.

[0158] The crude enzyme solution was added to a reaction system containing 100 mM TES-NaOH (pH 7.7), 5 mM MgCl<sub>2</sub>, 0.2 mM Coenzyme A, 0.3 mM cocarboxylase, 1 mM  $\alpha$ -ketoglutaric acid, 3 mM L-cysteine and 1 mM acetylpyridine-adenine dinucleotide, and absorbance at 365 nm was measured at various temperatures (30, 40, 50, 60 or 70°C) by a Hitachi spectrophotometer U-3210. The crude enzyme solution was pretreated at 50°C (pretreatment time: 1, 3, 5 or 10 minutes), and the activity was measured at 37°C. The results are shown in Fig. 15.

[0159] As a result, while ODHC of the 2256 strain was completely inactivated by the pretreatment for 10 minutes, ODHC of the AJ12310 strain showed substantially constant activity irrespective of the pretreatment time, and thus its stability against high temperature treatment was confirmed.

Table 14

Component	Concentration
Glucose	80 g/l
KH <sub>2</sub> PO <sub>4</sub>	1 g/l.
MgSO <sub>4</sub> ·7H <sub>2</sub> O	0.4 g/l
FeSO <sub>4</sub> ·7H <sub>2</sub> O	0.01 g/l
MnSO <sub>4</sub> ·7H <sub>2</sub> O	0.05 g/l
(NH <sub>4</sub> ) <sub>2</sub> SO <sub>4</sub>	30 g/l
rotein Soybean protein hydrolysate	480 mg/l
Thiamin hydrochloride	200 μg/l
Biotin	300 µg/l

# Example 5: Impartation of sucrose assimilating ability by gene transfer of scrB gene

[0160] Since the Corynebacterium thermoaminogenes AJ12310 strain did not have invertase activity and sucrose assimilating property, it was investigated if sucrose assimilating ability could be imparted to it by transferring the scrB gene of the AJ12309 strain to the strain.

<1> Production of plasmid carrying scrB derived from Corynebacterium thermoaminogenes AJ12309 strain

[0161] To obtain an scrB gene fragment, the primers shown in SEQ ID NOS: 101 and 102 were synthesized, of which both ends were ligated with Smal sequences, based on the nucleotide sequence shown in SEQ ID NO: 93. Sterilized water was added to  $0.5~\mu g$  of chromosomal DNA of the 12309 strain, 50 pmol each of the aforementioned oligonucleotides,  $4~\mu l$  of dNTP mixture (2.5 mM each),  $5~\mu l$  of 10 x Pyrobest Buffer (Takara Shuzo) and 2 U of Pyrobest polymerase (Takara Shuzo) to prepare a PCR reaction mixture in a total volume of 50  $\mu l$ . PCR was performed with a cycle of denaturation at 98°C for 10 seconds, association at 55°C for 30 seconds and extension reaction at 72°C for 2 minutes, which was repeated for 30 cycles, by using the above reaction mixture and a thermal cycler GeneAmp PCR System 9600 (PE) to amplify a fragment of about 1.7 kb containing scrB ORF.

[0162] Then, the above amplified fragment was digested with *Smal* (Takara Shuzo), and ligated to plasmid pSAC4 containing a dephosphorylated replication origin functioning in coryneform bacteria, which had been digested with *Smal*, to prepare pSCR155. The construction of pSCR155 is shown in Fig. 16. pSAC4 was produced as follows. In order to make the vector for *Escherichia coli* pHSG399 (Takara Shuzo) autonomously replicable in coryneform bacteria, the replication origin (Japanese Patent Laid-open No. 5-7491/1993) derived from the already obtained plasmid pHM1519 autonomously replicable in coryneform bacteria (Miwa, k.et al., Agric. Biol. Chem., 48 (1984) 2901-2903) was introduced into it. Specifically, pHM1519 was digested with restriction enzymes *Bam*HI and *KpnI*, and the obtained fragment containing the replication origin was blunt-ended by using a Blunting kit produced by Takara Shuzo and inserted into pHSG399 at the *Sall* site by using an *Sall* linker (produced by Takara Shuzo) to obtain pSAC4.

<2> Transfer of plasmid carrying scrB gene into AJ12310 strain

[0163] pSCR155 produced above and plasmid pSSM30BS (Japanese Patent Laid-open No. 08-196280/1996) carrying the scrB gene derived from Brevibacterium lactofermentum were introduced into the Corynebacterium thermoaminogenes AJ12310 strain. The transformation was performed according to the following procedure. The cells were inoculated to CM-2B medium containing 20% sucrose in such an amount that  $OD_{660}$  of the medium should become 0.1, and cultured at 37°C with shaking until the  $OD_{660}$  become 0.3. Lysozyme was added to the medium at a concentration of 100  $\mu$ g/ml, and the cells were further cultured for 2 hours. The cells were washed three times with 20% sucrose, suspended in 20% sucrose, added with the plasmid collected from Escherichia coli JM110, mixed sufficiently, and applied with an electric pulse (18 kV/cm, 300 msec) to be introduced with the DNA. After the cells were subjected to restoration culture overnight in CM-2B medium containing 20% sucrose, transformants were selected on CM-2B agar medium containing 5  $\mu$ g/ml of chloramphenicol. Specifically, the transformation was performed by the electric pulse method (Japanese Patent Laid-open No. 12-204236/2000, and the selection of transformants was performed

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on CM2B plate medium containing 5 µg/ml of chloramphenicol at 37°C. As a result, any transformant harboring the plasmid pSSM30BS carrying *scrB* derived from *Brevibacterium lactofermentum* was not obtained, but only a transformant harboring the plasmid pSCR155 carrying *scrB* derived from *Corynebacterium thermoaminogenes* was obtained. This strain was designated as AJ12310/pSCR155.

<3> Evaluation of culture of AJ12310/pSCR155 strain using sucrose as sugar source

[0164] AJ12310/pSCR155 prepared above was inoculated to a medium having the composition shown in Table 15, and cultured at 37°C for 22 hours with shaking. The absorbance (OD) and residual sugar (RS) of the medium were measured after the culture. The results are shown in Table 16. As a result, it was confirmed that, while the AJ12310 strain could not assimilate sucrose and hence could not grow, the *scrB* gene introduced strain, the AJ12310/pSCR155 strain, became to be able to assimilate sucrose.

Table 15

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tion
Concentration
60 g/l
1 g/l
.0.4 g/l
0.01 g/l
0.01 g/l
30 g/l
480 mg/l
200 μg/l
300 μ <b>g</b> /l

Table 16

Result of sucrose culture		
OD (x 51) RS (g/l)		
2256	1.292	0.00
AJ12310	0.058	60.00
AJ12310/pSCR155	1.571	0.84

Example 6: L-glutamic acid production by pdhA gene-amplified strain

<1> Construction of plasmid pPDHA-2 carrying pdhA

[0165] The pdhA gene derived from the Corỳnebacterium thermoaminogenes AJ12310 strain was obtained by screening of a plasmid library. Specifically, PCR was performed with the conditions shown in Example 1, Table 4, using a plasmid library mixture as a template, and a clone p21A was selected, from which a DNA fragment of the same size is amplified as obtained in PCR using chromosomal DNA as a template. The DNA sequence of this plasmid was determined to confirm that the full length of pdhA was contained in it.

[0166] p21A was digested with Xbal and Kpnl to excise a DNA fragment of 4 kb containing the full length of the pdhA gene and a promoter region. This DNA fragment containing the pdhA gene was inserted into the Xbal and Kpnl sites of pHSG299 (Takara Shuzo). Then, this plasmid was digested with Xbal, and a fragment obtained by digesting pXK4 with Xbal was inserted to prepare pPDHA-2. The construction process of pPDHA-2 is shown in Fig. 17. A DNA Ligation Kit Ver.2. (Takara Shuzo) was used for the ligation reaction, and Escherichia coli JM109 strain (Takara Shuzo) was used as the host of genetic manipulation. The aforementioned pXK4 was produced as follows. A shuttle vector pHK4 for coryneform bacteria and Escherichia coli (Japanese Patent Laid-open No: 5-7491/1993) was digested with restriction enzymes BamHI and Kpnl to obtain a DNA fragment containing the replication origin, and the obtained fragment

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was blunt-ended by using a DNA blunting kit (Blunting Kit produced by Takara Shuzo), ligated to an Xbal-linker (produced by Takara Shuzo) and inserted into pHSG299 at the Xbal site to obtain the plasmid pKX4.

<2> Transfer of plasmid carrying pdhA gene into AJ12310 strain

[0167] The plasmid pPDHA-2 produced above was introduced into the *Corynebacterium thermoaminogenes* AJ12310 strain to prepare a *pdhA* gene-amplified strain. The transformation was performed in the same manner as Example 5, and a transformant was selected on CM-2B agar medium containing 25 µg/ml kanamycin to obtain AJ12310/pPDHA-2 strain.

<3> L-glutamic acid production by pdhA-amplified strain

[0168] The AJ12310 strain and the *pdhA* gene-amplified strain obtained above, AJ12310/pPDHA-2 strain, both of which were grown on CM-2B agar medium, were each inoculated to a 500-ml volume flask containing 20 ml of a medium for seed culture flask shown in Table 17, and cultured at 37°C with shaking until glucose was completely consumed. 2 ml of this culture broth was inoculated into 500 ml-volume flask containing 20 ml of a medium for main culture flask shown in Table 17, and cultured as main culture at 37°C and 44°C. The main culture was continued until glucose was completely consumed. After the culture, OD<sub>620</sub> of the medium and accumulated amount of L-glutamic acid were measured to examine the effect of the gene amplification on the cell formation and production of glutamic acid. The measurement of OD was performed by using a spectrophotometer HITACHI U-2000 (Hitachi), and L-glutamic acid concentration was measured by using a glutamic acid analyzer AS-210 (Asahi Chemical Industry). The results are shown in Fig. 18.

**[0169]** The *pdhA* gene-amplified strain, AJ12310/pPDHA-2 strain, showed increased L-glutamic acid accumulation and increased OD compared with the AJ12310 strain, and thus it became clear that the amplification of the *pdhA* gene was effective for L-glutamic acid production.

Table 17

Medium for evaluation of pdhA-amplified strain		
Medium composition	Seed culture	Main culture
Sucrose	30 g/l	60 g/l
KH <sub>2</sub> PO <sub>4</sub>	1 g/l	1 g/l
MgSO <sub>4</sub> ·7H <sub>2</sub> O	0.4 g/l	0.4 g/l
FeSO <sub>4</sub> ·7H <sub>2</sub> O	0.01 g/l	0.01 g/l
MnSO <sub>4</sub> ·7H <sub>2</sub> O	0.01 g/l	0.01 g/l
(NH <sub>4</sub> ) <sub>2</sub> SO <sub>4</sub>	15 g/l	30 g/l
Soybean protein hydrolysate	480 mg/l	480 mg/l
Thiamin hydrochloride	200 μg/l	200 μg/l
Biotin	10 μg/l	
AZ-20R (anti-foaming agent)	20 μg/l	20 μg/l
CaCO <sub>3</sub> (separately sterilized)	50 g/L	50 g/L
pH 8.0 (adjusted with KOH)		1

Example 7: L-glutamic acid production by icd gene-amplified strain

<1> Construction of plasmid pICD-4 carrying icd derived from Corynebacterium thermoaminogenes AJ12310 strain

[0170] Based on the *icd* gene sequence of the AJ12310 strain shown in SEQ ID NO: 29, the primers shown in SEQ ID NO: 103 and SEQ ID NO: 104 were synthesized. A *Bgl*II site was introduced into 5' end of the both primers. Separately, genomic DNA of the *Corynebacterium thermoaminogenes* AJ12310 strain was prepared by using a Genomic DNA Purif. Kit (Edge BioSystems). Sterilized water was added to the genome DNA as a template, 100 pmol each of the aforementioned primers, 8 μl of dNTP mixture (2.5 mM each), 10 μl of 10 x Pyrobest Buffer II (Takara Shuzo) and

2.5 U of Pyrobest polymerase (Takara Shuzo) to prepare a PCR reaction mixture in a total volume of 100 µl. PCR was performed with a cycle of denaturation at 98°C for 10 seconds, association at 55°C for 1 minute and extension reaction at 72°C for 4 minutes, which was repeated for 30 cycles, by using the above reaction mixture and a thermal cycler TP240 (Takara Shuzo) to amplify a DNA fragment of about 3.3 kb containing the *icd* gene and its promoter.

[0171] Then, this DNA fragment containing the *icd* gene was digested with *Bgl*II, and ligated to pHSG299 (Takara Shuzo) at the *Bam*HI site. This plasmid was then treated with *Xba*I, and a fragment obtained by digesting pXK4 with *Xba*I was inserted into the plasmid to construct pICD-4. The construction procedure of pICD-4 is shown in Fig. 19. A DNA Ligation Kit Ver.2 (Takara Shuzo) was used for the ligation reaction, and *Escherichia coli* JM109 strain (Takara Shuzo) was used as the host of genetic manipulation.

<2> Transfer of plasmid carrying icd gene into AJ12310 strain

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[0172] The plasmid pICD-4 produced above was introduced into the *Corynebacterium thermoaminogenes* AJ12310 strain to prepare an *icd* gene-amplified strain. The transformation was performed in the same manner as Example 5, and a transformant was selected on CM-2B agar medium containing 25 µg/ml kanamycin to obtain AJ12310/pICD-4 strain.

<3> L-glutamic acid production by icd-amplified strain

[0173] Culture evaluation was performed for the AJ12310 strain and the *icd*-amplified strain thereof, AJ12310/pICD, by the culture method described in Example 6. The results are shown in Fig. 20. The *icd* gene-amplified strain AJ12310/pICD-4 strain showed increased L-glutamic acid accumulation and increased OD compared with the AJ12310 strain, and thus it became clear that the amplification of the *icd* gene was effective for L-glutamic acid production.

Example 8: L-glutamic acid production by *gdh* gene-amplified strain

<1> Construction of plasmid carrying gdh derived from Corynebacterium thermoaminogenes AJ12310 strain

[0174] Based on the *gdh* gene sequence of the AJ12310 strain shown in SEQ ID NO: 79, the primers shown in SEQ ID NO: 105 and SEQ ID NO: 106 were synthesized.

[0175] Separately, chromosomal DNA of the AJ12310 strain was prepared by using a Bacterial Genome DNA Purification Kit (Advanced Genetic Technologies Corp.). Sterilized water was added to 0.5 μg of this chromosomal DNA. 10 pmol each of the aforementioned oligonucleotides, 8 μl of dNTP mixture (2.5 mM each), 5 μl of 10 x LA Taq Buffer (Takara Shuzo) and 2 U of LA Taq (Takara Shuzo) to prepare a PCR reaction mixture in a total volume of 50 μl. PCR was performed with a cycle of denaturation at 94°C for 30 seconds, association at 55°C for 1 second and extension reaction at 72°C for 3 minutes, which was repeated for 30 cycles, by using the above reaction mixture and a thermal cycler TP240 (Takara Shuzo) to amplify a DNA fragment of about 2 kb containing the *gdh* gene and its promoter. The obtained amplified fragment was digested with *Pst*I (Takara Shuzo), mixed with pHSG299 (Takara Shuzo) fully digested with *Pst*I and ligated to it. A DNA Ligation Kit Ver.2 produced by Takara Shuzo was used for the ligation reaction. After the ligation, competent cells of *Escherichia coli* JM109 (produced by Takara Shuzo) were transformed with the ligation product, plated on L medium (10 g/I of Bacto-trypton, 5 g/I of Bacto-yeast extract, 5 g/I of NaCl, 15 g/I of agar, pH 7.2) containing 10 μg/ml of IPTG (isopropyl-β-D-thiogalactopyranoside), 40 μg/ml of X-GaI (5-bromo-4-chloro-3-indolyl-β-D-galactoside) and 40 μg/ml of chloramphenicol, and cultured overnight. The emerged white colonies were picked up and subjected to single colony separation to obtain transformants.

[0176] Plasmids were prepared from the transformants by the alkali method (Text for Bioengineering Experiments, Edited by the Society for Bioscience and Bioengineering, Japan, p.105, Baifukan, 1992) and their restriction maps were prepared. A plasmid having a restriction map equivalent to that shown in Fig. 21 was designated as pHSG299YGDH.

[0177] A replication origin that functions in coryneform bacteria was introduced into this pHSG299YGDH. Specifically, pXC4 was digested with a restriction enzyme *Xba*l to obtain a fragment containing a replication origin derived from pHM1519, and it was mixed with pHSG299YGDH fully digested with *Xba*l and ligated to it. Plasmids were prepared in the same manner as above and a plasmid having a restriction map equivalent to that shown in Fig. 21 was designated as pYGDH. pXC4 was constructed in the same manner as that for pXK4 mentioned in Example 6 except that pHSG399 (Cmf) was used instead of pHSG299.

<2> Transfer of plasmid carrying gdh gene into AJ12310

[0178] The plasmid produced above was introduced into the Corynebacterium thermoaminogenes AJ12310 strain

to prepare a *gdh* gene-amplified strain. The transformation was performed in the same manner as Example 5; and a transformant was selected on CM-2B agar medium containing 25 µg/ml kanamycin at 31°C to obtain AJ12310/pYGDH.

<3> L-glutamic acid production by gdh-amplified strain

[0179] The AJ12310 strain and the *gdh* gene-amplified strain obtained above. AJ12310/pYGDH strain, both of which were grown on CM-2B agar medium, were each inoculated to a 500-ml volume flask containing 20 ml of a medium for seed culture flask shown in Table 18, and cultured at 37°C with shaking until glucose was completely consumed. 2 ml of this culture broth was inoculated into 500 ml-volume flask containing 20 ml of a medium for main culture flask shown in Table 19, and cultured as main culture at 37°C and 44°C. The main culture was continued until glucose was completely consumed. After completion of the culture, OD<sub>620</sub> of the medium and accumulated amount of L-glutamic acid were measured to examine the effect of the gene amplification on the cell formation and production of glutamic acid. The measurement of OD was performed by using a spectrophotometer HITACHI U-2000 (Hitachi), and L-glutamic acid concentration was measured by using a glutamic acid analyzer AS-210 (Asahi Chemical Industry).

Table 18

Table 10	e de la companya de
Composition of medium for	seed culture
Medium composition	Concentration
Glucose	30 g/l
Ammonium sulfate	15 g/l
KH <sub>2</sub> PO <sub>4</sub>	1 g/l
MgSO <sub>4</sub> ·7H <sub>2</sub> O	0.4 g/l
FeSO <sub>4</sub> ·7H <sub>2</sub> O	0.01 g/l
MnSO <sub>4</sub> ·7H <sub>2</sub> O	0.01 g/l
Soybean protein hydrolysate	0.48 g/l
Thiamin hydrochloride	200 μg/l
Biotin	10 μg/l
AZ20R	0.02 ml/l
CaCO <sub>3</sub> (separately sterilized)	1 g/L
pH 8.0 (adjusted with KOH)	

Table 19

Composition of medium for main culture				
Medium composition	Concentration			
Glucose	60 g/l			
Ammonium sulfate	30 g/l			
KH <sub>2</sub> PO <sub>4</sub>	1 g/l			
MgSO <sub>4</sub> ·7H <sub>2</sub> O	0.4 g/l			
FeSO <sub>4</sub> ·7H <sub>2</sub> O	0.01 g/l			
MnSO <sub>4</sub> ·7H <sub>2</sub> O	0.01 g/l			
Soybean protein hydrolysate	0.48 g/l			
Thiamin hydrochloride	200 μg/l			
ĀZ20R	0.02 ml/l			
CaCO <sub>3</sub> (separately sterilized)	· 1 g/L			
PH 8.0 (adjusted with KOH)				

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[0180] The results of the culture are shown in Table 20 and Table 21. At 37°C, the gdh-amplified strain showed higher saccharide consuming rate, better growth and higher attained OD compared with the parent strain, the AJ12310 strain. Moreover, both of the L-glutamic acid accumulation and the yield were markedly improved, i.e., 5-7%, at 37°C. Also at 44°C, the yield was improved, and the attained OD increased. On the other hand, it was confirmed that accumulation of  $\alpha$ -ketoglutaric acid was decreased in the  $\alpha$ -amplified strain. These results demonstrate that the amplification of  $\alpha$ -dh is effective for improvement in L-glutamic acid yield and reduction of byproduct.

Table 20

Culture result of <i>gdh</i> -amplified strain (37°C)						
OD <sub>620</sub> L-Glu accumulation L-Glu yield (51x) (g/dl) (%)						
AJ12310	0.58	1.74	30.7	53.9		
AJ12310/PYGDH	0.65	2.23	39.3	4.1		

Table 21

Culture result of <i>gdh</i> -amplified strain (44°C)					
	L-Glu accumulation (g/dl)	L-Glu yield (%)			
AJ12310	0.63	1.70	26.7		
AJ12310/pYGDH	0.7,1	1.79	27.8		

Example 9: L-glutamic acid production by gltA gene-amplified strain.

<1> Construction of plasmid carrying gltA gene derived from Corynebacterium thermoaminogenes

[0181] Based on the *gltA* gene sequence of the AJ12310 strain shown in SEQ ID NO: 89, the primers shown in SEQ ID NO: 107 and SEQ ID NO: 108 were synthesized.

[0182] Separately, chromosomal DNA of the AJ12310 strain was prepared by using a Bacterial Genome DNA Purification Kit (Advanced Genetic Technologies Corp.). Sterilized water was added to 0.5 μg of this chromosomal DNA, 10 pmol each of the aforementioned oligonucleotides, 8 μl of dNTP mixture (2.5 mM each), 10 μl of 10 x Pyrobest-Taq Buffer (Takara Shuzo) and 2 U of Pyrobest Taq (Takara Shuzo) to prepare a PCR reaction mixture in a total volume of 100 μl. PCR was performed with a cycle of denaturation at 94°C for 30 seconds, association at 45°C for 30 seconds and extension reaction at 72°C for 3 minutes, which was repeated for 30 cycles, by using the above reaction mixture and a thermal cycler TP240 (Takara Shuzo) to amplify a DNA fragment of about 2 kb containing the *gltA* gene and its promoter. The obtained amplified fragment was digested with *Kpnl* (Takara Shuzo), mixed with pHSG299 (Takara Shuzo) fully digested with *Kpnl* and ligated to it. A DNA Ligation Kit Ver.2 produced by Takara Shuzo was used for the ligation reaction. After the ligation, competent cells of *Escherichia coli* JM109 (produced by Takara Shuzo) were transformed with the ligation product, plated on L medium (10 g/l of Bacto-trypton, 5 g/l of Bacto-yeast extract, 5 g/l of NaCl, 15 g/l of agar, pH 7.2) containing 10 μg/ml of IPTG (isopropyl-β-D-thiogalactopyranoside). 40 μg/ml of X-Gal (5-bromo-4-chloro-3-indolyl-β-D-galactoside) and 40 μg/ml of chloramphenicol, and cultured overnight. The emerged white colonies were picked up and subjected to single colony separation to obtain transformants.

[0183] Plasmids were prepared from the transformants by the alkali method (Text for Bioengineering Experiments, Edited by the Society for Bioscience and Bioengineering, Japan, p.105, Baifukan, 1992) and their restriction maps were prepared. A plasmid having a restriction map equivalent to that shown in Fig. 22 was designated as pHSG299YCS. [0184] A replication origin that is replicable in coryneform bacteria was introduced into this pHSG299YCS. Specifically, pXC4 was digested with a restriction enzyme *Xbal* to obtain a fragment containing a replication origin derived from pHM1519, and it was mixed with pHSG299YCS fully digested with *Xbal* and ligated to it. Plasmids were prepared in the same manner as above and a plasmid having a restriction map equivalent to that shown in Fig. 22 was designated as pYCS.

<2> Transfer of plasmid carrying gltA gene into AJ12310 strain

[0185] The plasmid produced above was introduced into the Corynebacterium thermoaminogenes AJ12310 strain

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to prepare a *gltA* gene-amplified strain. The transformation was performed in the same manner as Example 5, and a transformant was selected on CM-2B agar medium containing 25  $\mu$ g/ml kanamycin to obtain AJ12310/pYCS.

<3> L-glutamic acid production by gltA-amplified strain

[0186] The AJ12310 strain and the *gltA* gene-amplified strain obtained above. AJ12310/pYCS strain both of which were grown on CM-2B agar medium, were cultured in the same manner as in Example 8. The results of the culture are shown in Table 22 and Table 23. Both at the culture temperatures, 37°C and 44°C, the CS-enhanced strain showed improved glutamic acid accumulation compared with the parent strain. Further, the *gltA*-amplified strain showed decreased L-aspartic acid and L-lysine, which are synthesized from oxaloacetic acid.

[0187] These results demonstrate that the amplification of *gltA* is effective for improvement of L-glutamic acid yield and reduction of byproduct.

Table 22

Culture result of gltA-amplified strain (37°C)				
	L-Glu accumulation (g/dl)	Yield (%)	L-Asp accumulation (mg/dl)	L-Lys accumulation (mg/dl)
AJ12310	1.79	31.9	11.8	11.0
AJ12310/pYCS	2.04	36.5	8.1	7.3

Table 23

Culture result of <i>gltA</i> -amplified strain (44°C)					
	OD	L-Glu accumulation (g/dl)	Yield (%)	L-Asp accumulation (mg/dl)	L-Lys Accumulation (mg/dl)
AJ12310	0.58	1.38	21.8	23.3	29.2
AJ12310/pYCS	0.65	1.84	28.8	14.1	17.2

[Explanation of Sequence Listing]

# [0188]

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SEQ ID NO: 1: aceA, nucleotide sequence SEQ ID NO: 2: aceA, amino acid sequence SEQ ID NO: 3: accBC, nucleotide sequence SEQ ID NO: 4: accBC, amino acid sequence SEQ ID NO: 5: dtsR1, nucleotide sequence SEQ ID NO: 6: dtsR1, amino acid sequence SEQ ID NO: 7: dtsR2, nucleotide sequence SEQ ID NO: 8: dtsR2, amino acid sequence SEQ ID NO: 9: pfk, nucleotide sequence SEQ ID NO: 10: pfk, amino acid sequence SEQ ID NO: 11: scrB (AJ12340), nucleotide sequence SEQ ID NO: 12: scrB (AJ12340), amino acid sequence SEQ ID NO: 13: scrB (AJ12309), nucleotide sequence SEQ ID NO: 14: scrB (AJ12309), amino acid sequence SEQ ID NO: 15: scrB (AJ12310), nucleotide sequence SEQ ID NO: 16: gluABCD, nucleotide sequence SEQ ID NO: 17: gluABCD, amino acid sequence SEQ ID NO: 18: gluABCD, amino acid sequence SEQ ID NO: 19: gluABCD, amino acid sequence-SEQ ID NO: 20: gluABCD, amino acid sequence

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#### Industrial Applicability

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[0189] According to the present invention, genes coding for enzymes of amino acid biosynthetic pathway derived from Corynebacterium thermoaminogenes, or genes coding for proteins involved in the amino acid uptake into cells. [0190] The genes of the present invention can be utilized for the production of the aforementioned enzymes or proteins, or the breeding of amino acid producing bacteria.

#### \*EP 1 219 712 A15 중 역동

# SEQUENCE LISTING

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			345		•	٠.	100	350					355	· · ·			. 1	
	aag	atc	acc	cgc	tac	cgt	gag	ccc	gcċ	ggc	ccg	ggt	gtc	cgc	atg	gac	1698	
	Lys	He	Thr	Arg	Туг	Arg	Glu	Pro	Ala	Gly	<b>b</b> to	Gly	Val	Arg	Me t	Asp		
35		360				-	365		•	• -		3.70	·.			•		
	tcc	ggc	gtt	gtc	gag	ggt	tcc	gag	atc	tcc	ggc	cag	ttc	gac	tcc	atg	1.746	
	Ser	Gly	Val	Val	Glu	Gly	Ser	Glu	lle	Ser		Gln	Phe	Asp	Ser	Met		
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40	ctg	gcc	aag	ctg	atc	gtc	t gg	ggc	cag	acc	cgt	gag	cag	gcc	ctg	gag	1794	٠
	Leu	Ala	Lys	Leu	He	Val	Trp	·Gly		Thr	Arg	Glu	Gln	Ala		Glu		•
			,		395			٠.		400					405			
	cgt	tcc	cgt	cgt	gcg	ctc	ggc	gag	tac	atc	gtc	gag	ggc	atg	ccg	acc	1842	
45	Arg	Ser	Arg	Arg	Ala	Leu	Gly	Glu	Туг	He	Val	Glu	·Gly	Me t	Рго	Thr		
•				410				٠.	415					420				
•	gtc	atc	ccg	ttc	cac	tcc	cac	atç	gic	t c c	aac	ccg	gca	ttc	gtc	ggl	1890	
	Val	lle	Pro	Phe.	His	Ser	His	Ile	Vạl	Ser	Asn	Pro	Ala	Phe	Val	Gly	• • •	
50			425		•			430			e e		435		*			
	gaç	ggc	gag	ggc	ttc	gag	gto	tac	acc	aag	tgg	atc	gag	gag	gtc	l gg	1938	
•	Asp	Gly	Glu	Gly	Phe	Glu	Val	Туг	Thr	. Lys	Trp	I-l e	Glu	Glu	Va l	Trp		•
··	- 1. 	440		تسبيت			445					450						~
<i>55</i>	gac	aac	ccg	atc	gag	ccg	tto	gto	gat	gca	gcc	gac	cţc	gac	gac	gag	1986	
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	Asp As	n Pro	He	Glu	Pro 460		Val	Asp	Ala	Ala 465	Asp	Leu	Asp	Asp	Glu 470	
,	455 gag aa	a 200		100			atc	atc	atr.		atc	gar	gar	cac		2034
5	Glu Ly	_														2004
	Giu Ly	2 1111	110	475	GIH	Lys	, 41	110	480.		110	ASP		485	,	• •
	gtc ga	oroto	art		CCG	gge	·øac	ctc			ggr	ggi	ggi		ggt	2082
10	Val Gl															. 5005
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	gcc gc			220	ር ር p	ลลฮ	aag		cgc	gca	ggi	ggc		ลลg	gcc	2130
	Ala Al															
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	ggt gt			gac	tcc	gtc		gcc	ccg	atg	cag	ggc	acc	gtc	atc	2178
•	Gly Va															
•	52					525	•				530	•		. •	٠	
20 ·	aag gi	c aac	gtt	gag	gac	ggc	gcc	gag	gtc	tcc	gag	ggt	gac	acc	gtc	2226
	Lys Va	l Asn	Val	Glu	Asp	Gly	Ala	Ġlu	Va 1	Ser	Glu	Gly	Asp	Thr	Val	
	535			١.	540	•		-	•	545					550	
	gig gi	t ct-c	gag	gcc	alg	aag	atg	gag	aac	ccg	gtc	aag	gcc	ćac	aag	2274
25	Val Va	Leu	Glu	Ala	Met	Lys.	Met	Glu	Asn	Pro	Val:	Lys	Ala	His.	Lys	
				555			5.	1	560					565	• * •	•
•	tcc gg															2322
	Ser Gly	Thr		Ser	Gly	Leu	Thr		Ala	Ala	Gly	Glu		Val	Thr	
30		•	570			•	•	575			•		580			
	aag gg								iaai	l cc c	ttc	iggg	acag	ga		2369
	Lys Gly		Val	Leu	Leu	Glu		Lys			÷	•				**
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35	cagece	gtt	ct										. •			2381
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40 .	<211> {			•.									•			
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45	Val Ser	Val	Glu	Thr	Arg	Lys	He	Thr	Lys	Val	Leu-	Val	Ala	Asn	Arg	
	1			5	•										· i	٠.
	Gly Glu	He	Ala	He	Arg	Val	Phe	Arg	Ala	Ala	Arg	Asp	Glu	$\textbf{G}  \textbf{I} \cdot \textbf{y}^{\cdot}$	I'l e'	
			20		. :		•	25	•	•			30		. : :	
50	Ala Ser	Val	Ala	Val	Туг	Alá	Glu	Pro	Asp	Ala	Asp	Ála	Pro	Phe	Val	
	• ;	35		٠.			-40	٠.			•	45				
	Glu Tyr	Ala	Asp	Glu	Ala	Phe	Ala	Leu	Gly	Gly	Gln	$Thr\cdot$	Ser	Ala	Glu	
e.c.	50	)				55					60	•			٠.	
<b>5</b> 5	Ser Tyr	T					71.	T . 1		4.1	1811	A	1	C	Clu	

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	•	65	<b>.</b>	-A-1-a	Val	uio	Dec.	Clu	Tur	Gly	Phe	Ten:	Ala	Glu	Asn	Ala	Asp	•		
		-A-i-a	-A·S·P-	-A-1-a	-1-2-1	-л-ı-ऽ 85	r-1-u-	y		.U.I.Y	90	<u> </u>				95	<u> </u>	.;	-	
5		Dha	Ala	Glu	410	Val	Ϊλο	A c.n	Cin	Clv							Ser		•	
	, it is a	rne	Ala		100	vai	116	лэн	u i u	105	LUU	•••			110					
•		Ď	C1	Ser	The	A = G	Car.	I e u			Ivs	Val	Thr			His	He			
		Pro	GIU		116	HIE	361	LCu.	120	МЭР	2,0		• • • • • • • • • • • • • • • • • • • •	125						
10 .				115 Asn	Ala	A c n	112	Pro		Ala	Pro	Gľv			Glu	Рго	Val	,		
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		` *	130	Ala	Ala	C10	Val	Val	Δla	Phe	Ala	Glu		Phe	Glv	Leu	Pro	. **		
			ASD	на	ЛІА		150			1110	7,, 0	155	0.0			-	160		1.2	•
15		145	410	He	luc	 Δ l a	Ala	Dhe	Glv	Clv				Glv	Met:					
	CALL THE HIS	11.6	Ala	115	TAP	165	Üιa.	THE	Öı i	0.7	170	3.3	6		100	175	:			•
•		4.1.4	T	Glu	Mai	Acn	Glu	Va I	Ala	Asp		Phe	Glu	Ser	Ala	Thr	Arg			
•		Ala	1 7 1	010	180	V2:N	O i u	161		185	200				190		,	<u>.</u>		
20		Clu	Ala	Thr	100	Δία	Phe	Clv.	Arg		Glu	Cvs	Phe	.Val		Arg	Tyr.			
		Gru,	WIG	195		Ald.	1 11 C		200					205						
		Leu	Acn.	Tve	Ala	Arσ	His										His	-		
		Leu	210	Lys	Wid			215					220					•:		
25	:	Glv		Val	Val	Val	Ala			Arg	Asp	Cys	Ser	Leu	Gin	Arg.	Arg			•
		225	11311	141	141	ν,α.	230			7,7		235					.240		-	
		Phe	Gin	Lys	Len	Val			Ala	Pro	Ala		Phe	Leu	Thr	Asp	Glu			
30		The	.0111	ی رید		245		¥			250			٠.,		255				
	A.	Gln	Arg	Asp	Arg	He	His	Ser	Ser	Ala	Lys	Ala	He	Cys.	Arg	Glu	Ala			
					260					265		: : . :			270		· · · · · · · · · · · · · · · · · · ·			
		Glv	Tvr	Туг	Gly	Ala	Gly	Thr	Val	Glu	Tyr	Leu	Val	Gly	Ser	Asp	Gly		7. 3 <sup>1</sup>	•
35		*		275					280			٠.		285	*					
		Leu-	lle	Ser	Phe	Leu	Glu	Val	Asn	Thr	Arg	Leu	Gln	Val	Glu	His	Pro			
			290					295					300					- •		
٠.	*	Val	Thr	Glu	Glu	Thr	Thr	Gly	lle	Asp	Leu	Val	Arg	Glu	Met	Phe	Arg			
40	**	305					310					315	-				320		a 1.	
•		lle	Ala	Glu	Gly	Ala	Glu	Leu	Ser	lle	Lys	Glu	Asp	Pro	Thr	Pro	Arg			
						325					330	•				335				
		Gly	His	Ala	Phe	Glu	Phe	Arg	Ile	Asn	Gly	Glu	Asp	Ala	Gly	Ser	Asn			
45 .	es et est				340					345					:350			•	$v_{i} \in \mathbb{R}^{n} \times \mathbb{R}^{n}$	
. *-		Phe	Met	Pro	Ala	Pro	Glv	Lys	lle	Thr	Arg	Туг	·Arg	Glu	P 1 0	Ala	GIY			
				355	· : · · .		• ;		360					365			Car		· .	
*		Pro	Glv	Val	Arg	Met	· As n	Ser	Gly	y a i	y a ı	GIU	, GIY	261	GIU	1 1 1 1	261	** ( - 1		
50			370				. •	375					380	-		,, ,				
		C1.	Cln	Dho	Acn	742	Mot	1 61	ı Ala	Lvs	. J.eu	He	Val	Trp	- Gly	Gln	Thr			
		385	. •				390	٠. '			•	395		. •			400		•	
		_A.r.o	-G111	-Gl-n	_A.l.a	Leu	_ G.l.u	-Are	Ser	:_Arg	_Arg	Ala	Len	l 61 y	616	1 1 1 1 1	1116		<u>_</u> _ ·	_
55						405					410					415	1.12		• :	
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	Val Glu Gly Met Pro Thr Val IIe Pro Phe His Ser His IIe Val Ser 420 425 430
5	Asn Pro Ala Phe Val Gly Asp Gly Glu Gly Phe Glu Val Tyr Thr Lys 435 440 445
	Trp lle Glu Glu Vai Trp Asp Asn Pro Ile Glu Pro Phe Vai Asp Ala 450 455 460
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	Glu Ile Asp Gly Arg Arg Val Glu Val Ala Leu Pro Gly Asp Leu Ala
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	Ser Glu Gly Asp Thr Val Val Leu Glu Ala Met Lys Met Glu Asn
	545 550 555 560
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40	⟨221⟩ CDS
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	<b>&lt;400&gt;</b> 5
45	getgicalic egaceacati egeceegga leegggetee accaectee ggaceeatge 60
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	atccacctgt ggaacagtca gcggcgcggc catggagggc agcgacaggt gacgtccgag 180
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	Met Thr Ile Ser Ser Pro
	tig att gac gic gct aac cig cca gac atc aac acc acc gcc ggc aag 404
55	Leu Ile Asp Val Ala Asn Leu Pro Asp Ile Asn Thr Thr Ala Gly Lys

•						10		•			- 15				÷	20	٠,			
	··		-a-1-c	-g-c-c	-gac-		-a-a-e	-20C-	ege-	egg-	gcg_	gaa_	gcc_	_cac_	_t_t_c_	.C.C.C	atg	gg t_	452	· ·
		٠.	Tle	Ala	Asp	Leu	Lys	Ala	Arg	Arg	Ala	Glu	Ala	His	Phe	Pro	Met.	Gly		
5			•••		25	,				30			: .	21	35					
			gaa	aag	gcc	gta	gag	aag	gic	cac	gcg	gcc	aac	cgc	ctc	acc.	gcg	cgc	500	).
			Glu	Lys	Ala	Val	Glu	Lys	Val	His	Ala	Ala	Asn	Arg	Leu	Thr	Ala	Arg		
10			,	40			.,		45			٠.,		50	· . ·		•	1		•
			gaa	cœa	cll	gac	tac	cig	ctc	gat	gaa	ggc	tcc	tic	atc	gaa	acc	gat	548	} .
٠			Glu	Arg	Leu	Asp	Туг	Leu	Leu	Asp	Glu	Gly	Ser	Phe	lle	Glu	Thr	Asp		:
			55	:			* *.	60	* 1 1			•	65		t 1			. 70		
15			cag	ctc	gca	cgc	cac	cgc	acc	acc	gcg	ttc	ggc.	ctg	ggc	aac	aag	cga	596	5
			Gln	Leu	Ala	Arg	His	Arg	Thr.	Thr	Ala		Gly	Leu	Gly	Asn		Arg		
							75	1	• . •		٠.	80		•			85		C 4	. :
	•		ccg	gcc	acc	gac	ggc	atc	glc	acc	ggc	igg	ggc	acc	atc	gac	ggc	cgc	644	ł
20			Pro	Ala	Thr	Asp	Gly	He	Val	Thr		Trp	GIY	Inr	116	ASP	ыу	Arg		
			•			90					95		· -4-		t	100	<b></b>	c t c	691	)
		٠.	gag	gtc	tgc	atc	itc	tcc	cag	gac	ggc	acc	git	Dho	Clar	Clu	gla	LLL		٠. ، <u>٠</u>
	•		Glu	Vai		116	rne	ser	GIN	110		1111	Val	1 110	115	GIY	AIG.	Leu		i.,
25				_	105							a a o	alc	alo	_		gcc	atc	74	0
Ť			ggt	gag	gic	tac Tyr	ggt	Clu	luc	Mot	Ile	ive	lle	Met	Glu	Leu	Ala	Ile		
•			ыу	120	va i	1 9 1	GIY	Giu	125	m C i	110	2,5	110	130	•••	,200				
20				120	gar	cgc	cca	ctr		880	clg	tac	gag		gca	ggt	gcc	cgc	78	8
30	**		Acn	Thr	Clv	Arg	Pro	Leu	lle	Glv	Leu	Tyr	Glu	Gly	Ala	Gly	Ala	Arg		3 + 1
			135		013	111 6		140	- • •		,		145					150		
•			atc	cag	gac	ggt	gcg	gtc	t,c c	ctc	gac	ttc	atc	tcc	cag	acc	ttc	tat	83	6
35			He	Gln	Asp	Gly	Ala	Val	Ser	Leu	Asp	Phe	He	Ser	Gln	Thr	Phe	Туг		
					*		155		٠.			160					165			
			cag	aac	atc	cag	gcc	tcc	ggc	gtg	atc	ccg	cag	atc	tcc	gtg	atc	atg	88	4
			Gln	Asn	He	GIn	Ala	Ser	Gly	Val	He	Pro	Gln	He	Ser	Val	lle	Met		
40						170		•		•	175	, ;	. ,		•	180		1.11	. ;	
			ggt	gcc	tgc	gcc	ggl	ggc	a a c	gcc	tac	ggc	ccg	gcc	ctg	acc	gac	ttc	93	Ζ
			Gly	Ala	Cys	Ala	Gly	Gly	Asn	Ala	Tyr	Gly	Pro	Ala	Leu	lhr	ASD	Phe		
,					185					190					195					.0
45			glg	gtc	atg	gtg	gac	aag	acc	tcg	aag	alg	110	gio	acc	ggo	CCC	gat	98	٠.
			Val			Val	Asp	Lys			Lys	Met	Phe	val	Tur	GIY	rro	Asp		
				200	. '	· .	٠ .		205					210			- 010		1.0	28
50			glg	atc	aag	acc	gto	acc	ggo	gag	gag	alc	acc	cas	ggag	, Cr	s cro	ggc	1.0	140
50													IIII :			. GIL	ו רבח	Gly 230		
	٠,		215	٠.				220					225			. 134	. 200		,	76
			gga	gca	acc	acc	cac	alg	glo	aco	gco	gg(	, da(	, (0)	. Cat	. iai Tvi	. act	gtc Val		,
55			-Gly	Ala	T-h-r	-I-hr			v.a.:	I — I · II · I	A.1.6	240		i,	ئى قىلقى د م	,_ 4, <b>3</b> , 1	245	Val		
			•		•	•	235	,				240	,		•		270	•		

		gc	c ac	c ga	t gag	ggag	gco	: cto	gad	tg	ggt	c ca	g ga	ct	c : a t	c tec	tic	1124
		ΑI	a Ih	r Ası	p Gli	ı Gilu	Ala	Let	ı Asp			l Gl	n Ası	Lei			Phe	
5		٠,	~ ^^	: مفادة	250					255					260		. 1	* * *
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		LC	u ii	o Sei 265	. W21	7 1. ¥211	Λſģ	Sei	270		rrt	) ya	i GI			? Ąsp	Glu	
10		ga	g ga			atc	acc	σżα			300			275			ctg	1000
10	,3-a	GI	u Asi	p Gly	, Glv	lle	Ala	Gla	, аас Асп	ع ا	Thr	, gut	ga i	gac	CLE	aag	clg	1220
			28		013			285		116	1111		290		Leu	LYS	ren	. ,
		ga		galo	atc	ccg	gat				gto				ato		ma o	1260
15		Ası	p Gli	lle	Tle	Pro	Asp	Ser	Ala	Thr	Val	Pro	Tvr	Asn	Val	Aro	Aen	1268
		298	5				300	:			-	305				**** 6	310	**
		gto	ato	cag	tgc	ctg	acc	gac	gac	ggt	gag		,	gag	atc	cag		1316
		Val	116	Gln	Cys	Leu	Thr	Asp	Asp	Gly	Glu	Tyr	Leu	Glu	Ile	Gln	Ala	1010
20				•		- 315	-1		•		320		, .	100		325		e de la compa
		gao	cga	gcc	gag	aat	gtc	gic	atc	gcc	ttc	ggc	cgc	atc	gag	ggc	cag	1364
		Asp	Arg	Ala	Glu	Asn	Val	Val	He		Phe	Gly	Arg	Ile	`Glu	Gly	Gln	
								٠, ٠		335		•			340		• •	
25	. :	lcc	gic	ggt	ttc	gic	gcc	aac	cag	ccg	acc	cag	ttc	gcc	ggc	tgc	ctg	1412
		ser	va.ı	Gly 345	Pne	Yaı	Ala	Asn		Pro	Thr	Gln	Phe		Gly	Cys	Leu	
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30	,	Asn	lle	Asn	Ser	Cer	Clu	luc	gca	Ala	Cgc	Dha	gic	cgc	acc	tgc	ga t Asp	1460
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		gcc		aac	aic	ccg	atc.		aig	ctt	gtc	gar		CCC	ggr	110	CIC	1508
		Ala	Phe	Asn	He	Pro	He	Val	Met	Leu	Val	Asp	Val	Pro	Glv	Phe	Len	1308
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		ссс	ggt	gcc	ggc	cag	gag	tac	ggc	ggc	atc	cig	ċgt	cgt	ggc	gc c ·		1556
. :	:	Pro	Gly	Ala	Gly	Gln	Glu	Туг	Gly	Gly	He	Leu	Arg	Arg	Gly	Ala	Lys	
						395				:	400		•			405		
40		clg	ctc	tac	gcc	tac	ggt	gag	gcc	ac c	gtc	ccg	aag	atc	acc	gtg	acc	1604
		Leu	Leu	Tyr		Туг	Gly	Glu			Val	Pro	Lys	He	Thr	Val	Thr	
		. :			410	* *				415		, .	• • •	-	420			
45		atg	cgc	aag	gcc	tac	ggc	ggl	gcg	lac	lgl	gtc	atg	gga	tcc	aag	ggt	1652
		Mei	Arg	Lys	Ala	Гуг	Gly				Cys	Val			Ser	Lys	Gly	
				425					430					435			* * * *	
		tou	ggc	gca	gac	aic .	aac	clg	gcc	igg	ccg	acc	gcg	cag	atc	gcc	gtc	1700
50	·. ·	rtn	440	Ala	ush	116		Leu 445	Ala	1LD	110				11e	Ala	Val	
		a t o		acc	arr i	aar i				110	212		450				· ·	
		Met	Giv	gcc Ala	Ala	666 ) 610 )	SUB Mari	gil Val	cag Cin	Lit C Dha	aic Ila	Tu-	Vr~	aag	gag.	CIC	alg	1748
		455	J 1 J	nia .			160		GIII	1116		19T		r A 2	olu			. " ,
55			gel	gat						300				arr	c a ~		470	1796
		900	0.	Par	P	u.u.b. (	55	CIB	506	a C C	BIC	RCC	CIE	gcc.	cag	ıcc	i i C	1796

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10	Arg Gly Leu Ile Asp Ala Val Ile Leu Pro Ser Glu Thr Arg Gly Gln	
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•	lle Ala Arg Asn Leu Arg Leu Leu Lys His Lys Asn Val Ser Arg Pro	**
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•	Ala Arg Lys His Gly Asn Met Pro Leu	
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	Gly Thr lle Asp Gly Arg Glu Val Cys Ile Phe Ser Gln Asp Gly Thr	•
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	lle Met Glu Leu Ala lle Asp Thr Gly Arg Pro Leu Ile Gly Leu Tyr	$t^{\prime}$ .
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55	Glu Gly Ala Gly Ala Arg Ile Gln Asp Gly Ala Val Ser Leu Asp Phe	

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J		Gln	He	Ser	Val												Gly	
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	Pro Tyr Leu Ala Ala Glu Arg Gly Leu Ile Asp Ala Val Ile Leu Pro 500 505 510
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	lle Glu Tyr Leu Leu Asp Glu Gly Ser Phe Val Glu Val Asp Ala Leu 55 60 65
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55	Thr Asp Gly Val Val Thr Gly Tyr Gly Thr lle Asp Gly Arg Lys Val

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25	luc	Sar	Tur	Clv	Clv.	Ala	Tvr.	Cvs	Val	Met	Gly	Ser	Lys	Asp	Met	Gly	
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	Grii Ale	a Ser Val (	JIU LYS Y	al HIS GI	u Ala Gi	y Lys Ly	's Thr Al	la Arg
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25		As	p Gl	u Ası	p IIe	e Ası	о Ага	lle	Len	, Cit	, 650 1 Ara	. 65 ·	Ch	ነ ፈርረ ጉጉ	1 di(	Cig	ggc	544	1
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		ac	c gg	t cg	t cto	c cac		gac			. 202	ar.	ggs		, , , , , ,			592	
		Th	r GI	у Ага	z Lei	His	Рго	Aso	l.vs	Phe	Аго	A 1 a	659 Clv	116	gac	cag	gic	592	
30			7	5				80	-,0			,,,,,,	85		H2D	GIN	vai		
		aag	ggc	gaat	cto	gco	gat			áli	gac	or a	ctc	210					4
		Lys	. Ala	a Asn	Leu	Ala	Asp	Ala	Glv	He	Asn	Ala	Len	مان مان	Dea	dic	ggt	- 640	
		90	)				95					100		\11C	110	1.16			
35		gg	gag	ggc	acc	ctc						cic	ac.	ga c	220		105	COO	
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					• .	110				-,,	115		7110	nsp		120:			
		ccc	gtg	gtc	gg t	gic	ccg	aaa	acc	atc	gac.	aat	gal	ote	330	. 120.	000		ž .
40		Pro	Val	Va I	Gly	Val	O19	Lys	Thr	He	Asp	Asn	Asn	Val	Acn	Clu	The	736	
	•				125					130			,		135	,ui y	1111		3 F.
		gat	ite	acc	ttc	ggt	lic	gal	tcc			tet	plo	orr.	300		acc	701	
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		atc	gac	cgg	clg	cac	acc	acg		gaa	tee	cac	aar	col	ata	ator	210	022	
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		170				•	175			3	- 1.0	180	1 4		1113				
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55		Met	Ala	Gly	Glv	Ala	His	Tvr	The	Val	110	Dra	646 Clu	5.15 Val	D	LLC ) Dha	Rac	, 928	
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		,			1.90	. :		٠	••.	195		, ,		•	200		
<del></del>	alc	tro	gag	atc	igc	aag	cg t	a-tig-	gaa-	-c·g·t-	-egc-	-l-l-c-	-cag-	-a-t-g-	-ggg-	gag	976
* ·	I)e	Ser	Cla	He	Cvs	Lvs	Arg	Met	Glu	Arg	Arg	Phe	Gln	Met	Gly	Glu	The state of the
5	110	501	010	205		,		• :	210					215		,	
	220	tac	aar.	atc	atc	gtc	gic	gcg	gag	ggt	gcc.	ctg	ccc	aag	gag	gga	1024
	Inc	Туг	Clv	He	Ile	Val	Val	Ala	Glu	Gly	Ala	Leu	Pro	Lys	Glu	Gly	
	rys	. 1 9 1	220	110	110			225		a li			230		: :		
10.	300	alg	720	cla	.cōt	gag	ggg	gag	gtg	ġat	cag	110	ggt	cac	aag	acc	1072
	The	Met	Clu	Len	Aro	Glu	Glv	Glu	Val	Asp	Gln	Phe	Gly	His	Lys	Thr	
4.1.	1111	235		Lcu	111.6		240			•	1.1	245	1				
	110	200	aac	atc	Ø Ø C	cag			gcc	gac	gag	glg	cac	agg	cgt	cig	1120
15	Pho	Thr	Cly	Ile	Clv	Gin	Gln	Tle	Ala	Asp	Glu	Yal	His	Arg	Arg	Leu	
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	gg i	His	Acn	Val	Aro	Thr	Thr	Val	Leu	Glv	His	lle	Gln	Arg	Gly	Gly	
20	GIY	піз	ASP	741	270				-	275				4	280	1	
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	The	. ссс Рго	The	Ala	Phe	Asn	Arg	Val	Lèu	Ala	Thr	Arg	Туг	Gly	Val	Arg	
	· 1111	rio	1 111 1	285		7139	**** 5		290		٠.			295			\$ <b>*</b>
25 `	500	gcg	recort	gee	toc	rac :	gag	ggt			aac	acc	gtg	gtc	gcg	c.t.c	1264
	Ala	Als	. Δεσ	Δla	Γvs	His	Glo	Glv	Gln	Phe	Asn	Thr	Val	Val	Ala	Leu	
•	Ala	LVI	300					305					310		٠.		
	000		טטט ספס ד	הסר	ato		ats			tto	gal				ggc	acc	1312
30:1	lve	5 666 (1)	, 61 ii	Агр	Ile	Arg	Met	i Ile	Ser	Phe	Asp	Glu	Ala	Val	Gly	Thr.	
	Lys	315					320	)				325	· · · · ·		1		
	cts	7 22¢	, , , , , ,	r ete	7 TO 0.9	z ats	z ga	a cge	. igg	ggtg	acc	gcc	cag	gect	atg	ilc	1360
	lei	i Ivo	i Ivs	Val	Pro	Me 1	Glu	ı Arg	Trp	Val	Thr	Ala	Gln	Ala	Met	Phe	
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	991	t tag	ztcas	gcc				ttcci	gcgc	c go	gggg	ccgg	grig til	1111	cat	· · · .	1413
	Cly																
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		atta	teag	acci	ggta	tcc	gccc	ggtc	gt g	gacg	agite	gg	ccca	gcgg		• :	1643
	66			•••	0.5		•					- ;			*.		• 2
45	<b>1</b> 29	10>	10						• .				-				
	,	11>															
		12>		:					. '	, ,				•	٠.		
50		13>		neba	cler	ium	ther	moam	inog	enes				•			
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		00>	10		. :												
	N <sub>0</sub>	1 (1)	v'Al	a Me	t Ar	gIl	e Al	a Th	r Le	u Th	r- Se	r, Gl	y Gl	y As	р Су	s Pro	
55		.i0.i. 1	.y M.L.	w111_C		5				1	0				1	5	
55		1				-											

# EP 1 219 712 A11 1 5.4

*	G1	y Leu	Asn Ala 20	Val II	e Arg G	ly Ile 25	Val Arg	Thr Ala		n Glu
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	Ala	a Asp 1 50	Arg Arg	/al Glr	Leu T		Asp Glu	Asp Ile	Asp Ar	
10	Lei 68	ıLeu/	Arg Gly (	Sly Thr 70	lle L	eu Gly	Thr Gly	Arg Leu	His Pr	0 Asp
			Arg Ala (	85		ln Val	Lys Ala 90		0.0	o Ala
. 15			Asp Ala L 100			105		;	Leu Lys	Gly
20		' 1	rp Leu A 15	la Asp	Asn Gl	y Ile O	Pro Val	Val Gly	Val Pro	
20 .		11e A 130	SD ASN A	sp Val	Asn Gl 135	y Thr	Asp Phe	Thr Phe	Gly Phe	
25	140		al Ser V	150			155	4.	A 40 M	160
		,	er His A	5	٠.	1	170	• • •	175	•
30	·		rp Ile A 180	*		185			190	
	*	19		* * *	20	) '		205	• • • • • • •	
35		210	g Arg Ph		215		. 2	20	1	1.
	225		y Ala Le	230			235			240
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			p Glu Va 260 y His II			265			70	
<b>45</b> .		273	5 a Thr Arg		280		•	285		
	. 4	290	Asn Thi	Ż	295	-	30	00		•
50	305			310		` `	315			320
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*55* 

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         Trp Ala His Thr Thr Pro Leu Thr Gly Pro Gln Arg Leu Gln Trp
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         acg cac cig ccc gat gct cit tac ccg gat gta icc tal gac cig gal
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                                     40
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25
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                                                       60
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                                                                            240
30
         Phe Tyr Thr Gly Asn Arg Lys Ile Asp Gly Lys Arg Arg Ala Thr Gln
                                                   75
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         aac ctc gtc gaa gtc gag gac cca act ggg ctg atg ggc ggc att cat
                                                                            288
         Asn Leu Val Glu Val Glu Asp Pro Thr Gly Leu Met Gly Gly Ile His
35
                                               90
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         cgc cgc tcg cct aaa aat ccg ctt atc gac gga ccc gcc agc ggt ttt
                                                                            336
         Arg Arg Ser Pro Lys Asn Pro Leu lle Asp Gly Pro Ala Ser Gly Phe
                                                              110
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                     100
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         Thr Pro His Tyr Arg Asp Pro Met Ile Ser Pro Asp Gly Asp Gly Trp
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                 115
         aag aig git cit ggg gct cag cgc gaa aac cic acc ggt gca gcg git
                                                                             432
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                                  135
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         Leu Tyr Arg Ser Ala Asp Leu Glu Asn Trp Glu Phe Ser Gly Glu Ile
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			i.		2.0					25					30	٠.		•
5	2.5	300	cac	ctg	ccc	gac	gct	ctt	tac	ccg	gat	gca	tcc	tat	gac	ctg ·	gat	144
 		The	Uic	Leu	Pro	Asn	Ala	I.eu	Ťντ	Pro	Asp	Ala	Ser	Tyr	Asp	Leu	Asp	
,		1 11 1	H 1 2	35	1,10	nap	71.1 W		40		-	•		45				
				tat		+	aan	GCC'		111	act	gar	ggc.	aca	ctt	aaa	ctt	192
10		gga	tgc	lai	icc	ggı	gga	git	Val:	Dho	The	Acn	Clv	Thr	T en	Ivs	Leu	
	•	Gly		Tyr	Ser	Gly	GIY	Ala	Yaı	rne	1111	лзр	617	1111	Dea	بدريد	200	
			50		•			55					00			ناممة		240
	-	ttc	tac	acc	ggc	aac	cta	aaa	att	gac	ggc	aag	cgc	ege.	gee	The	C1-	240
15		Phe	Tyr	Thr	Gly	Asn	Leu	Lys	He	Asp	Gly	Lys	Arg	Arg	Ala	inr	GIN	
	-	65				-:	70					. 75.					, 8U.,	
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20		usn	200			85					90				,	95		
20		. ~ .	cat	tcg	cc t	222	aat	. ccg	ctt	atc	gac	gga	CCC	gcc	agc	ggt	ttc	336
	,	tgt • • •	Lg.	Ser	Dra	lve	Acn	Pro	Len	He	Asp	Glv	Pro	Ala	Ser.	Gly	Phe	
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			•	cat	100		4		2 1 0			cct	σat	e egt	gat	ggt	tgg	384
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	t	Thr	Pro	His	Туг	Arg	ASP	Pro	Mer	116	261	110	тэр	125	тор			•
				115	٠.				120			- 4 -				707	or t. t	432
		aaa	atg	gtl	ctt	ggg	gcc	caa	cgc	gaa	aac	CIC	acc	ggı	gta	gcg	git	402
30		Lys	Met	Val	Leu	Gly	Ala	Gln	Arg	Glu	Asn	Leu	lnr	GIY	Ala	Ala	var	
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		Leu	Tvi	Arg	Ser	Thi	Asp	Lei	ı Glu	Asn	Trp	Glu	Phe	Ser	Gly	Glu		
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				.*	**												•	
		<b>121</b>	0>	14										<u>.</u>				
		-	1>							*								
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		<40	00>	14							<b>.</b>	, <b>41</b> -	D	1	N = ~	. Th-	Clu	
45		Туз	Ту	r Glir	His	s Ası	o Pro	o Gi	y Phe	e Pro	Phe	e Ala	Pro	Lys	Arg	1111	Gly	
				.:		!	5	•		.*	10			. '		15		
		Tri	Al:	a His	Thi	Th	r Th	r Pr	o Lei	ı Thi	Gly	Pro	Gln	Arg	Leu	Gin	Trp	
*					20	)		•		28	Ó		• •		30	,		
50		Th	- Ні	s Lei	ı Pro	n Ası	o Al	a Le	и Туг	r Pro	a Ass	o Ala	ı Ser	Тут	Asp	Leu	Asp	
	•			35					4(	0				45	,			
		<u>ر ا</u>		O Tur	, - Co	- C1-	v GI:	ν ΔΙ			e Th	r Ası	o Glv	Thi	Lei	ı Lys	Leu	
		<u> </u>			36		<del>,</del> 01		5				60	) <del></del>	:			
<b>5</b> 5	-		) - ~	0	_ ^1	A -										Thi	Gln	• • •
	. •	Ph	e. Iy	r in	r 61	y AS	и ге	u Ly	S 111	r val	ָנט ק	, <i>1</i> , 3,	, ,,, 6					

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				acccigacai			
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w				ctattgagct			
				cigaccigig			
	· =			ggatttaccc			-
20				cacccg atg			654
					Ile Lys Met		
				1		5	• • •
	gig cag aas	tto tto g	at gac ttc	cag gcc ctg	acc gat ato	aat ctt	702
25				Gln Ala Leu			
· · · · · · · · · · · · · · · · · · ·		10		15	20		
• .	gag gir cco	grø gga c	ag gic gii	gtt gtt ctc	ggc ccg tcc	ggt tcc	750
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				Ala Kin-Gin			
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	sca cag clo	ILE EEL E	ss cas cas.	Lag Lac Big	bec are get	, , , , , , , , , , , , , , , , , , , ,	1000
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35	Ali	a Val 260	Leu	Ala	Gly	Ile	Thr 265	Leu	Thr	Ala	Cys	Gly 270	Asp	Ser	Glu	Gly	1529
35	Al	a Val 260 I gac	Leu ggt	Ala	Gly	Ile gcc	Thr 265 gcc	Leu atc	Thr gaa	Ala	Cys ggc	Gly 270 aat	Asp gtc	Ser	Gluatc	Gly	1529
35	gg Gl	a Val 260 t gac y Asp	Leu ggt	Ala	Gly ctc Leu	lle gcc Ala	Thr 265 gcc	Leu atc	Thr gaa	Ala	Cys ggc	Gly 270 aat	Asp gtc	Ser	Gluatc	Gly	- 147 - 147
	gg Gl: 278	260 t gac y Asp	Leu ggt Gly	Ala ctg Leu	Gly ctc Leu	Ile gcc Ala 280	Thr 265 gcc Ala	Leu atc Ile	Thr gaa Glu	Ala aat Asn	Cys ggc Gly 285	Gly 270 aat Asn	Asp gtc Val	Ser acc Thr	Glu atc Ile	Gly ggc Gly 290	- 147 - 147
35 40	gg Gly 278	a Val 260 t gac v Asp c aag	ggt Gly tac	Ala ctg Leu gat	Ctc Leu cag	gcc Ala 280 ccg	Thr 265 gcc Ala	Leu atc Ile	Thr gaa Glu gga	Ala aat Asn	ggc Gly 285 cgt	Gly 270 aat Asn	Asp gtc Val	Ser acc Thr	Glu atc Ile aat	ggc Gly 290 tcc	- 147 - 147
	gg Gly 278	260 t gac y Asp	ggt Gly tac	Ala ctg Leu gat Asp	Gly ctc Leu cag Gln	gcc Ala 280 ccg	Thr 265 gcc Ala	Leu atc Ile	Thr gaa Glu gga	Ala aat Asn	ggc Gly 285 cgt	Gly 270 aat Asn	Asp gtc Val	Ser acc Thr	Glu atc Ile aat	ggc Gly 290 tcc	1577
	gg Gly 279 acc Thi	a Val 260 t gac y Asp c aag Lys	ggt Gly tac Tyr	Ala ctg Leu gat Asp	Gly ctc Leu cag Gln 295	gcc Ala 280 ccg Pro	Thr 265 gcc Ala ggt Gly	Leu atc Ile ctg	Thr gaa Glu gga Gly	aat Asn ctg Leu 300	ggc Gly 285 cgt Arg	Gly 270 aat Asn aac Asn	Asp gtc Val ccg Pro	Ser acc Thr gac Asp	Glu atc Ile aat Asn 305	ggc Gly 290 tcc Ser	1577
40	gg Gly 27: acc Thi	a Val 260 t gac y Asp c aag Lys	ggt Gly tac Tyr	Ala ctg Leu gat Asp	Ctc Leu cag Gln 295 gat	gcc Ala 280 ccg Pro	Thr 265 gcc Ala ggt Gly	atc lle ctg Leu	Thr gaa Glu gga Gly gcg	aat Asn ctg Leu 300	Cys ggc Gly 285 cgt Arg	Gly 270 aat Asn aac Asn	Asp gtc Val ccg Pro	Ser acc Thr gac Asp	atc lle aat Asn 305	ggc Gly 290 tcc Ser	1577 <sup>2</sup> 1625
	gg Gly 27: acc Thi	a Val 260 t gac y Asp c aag Lys	ggt Gly tac Tyr	Ala ctg Leu gat Asp	Ctc Leu cag Gln 295 gat	gcc Ala 280 ccg Pro	Thr 265 gcc Ala ggt Gly	atc lle ctg Leu	Thr gaa Glu gga Gly gcg	aat Asn ctg Leu 300	Cys ggc Gly 285 cgt Arg	Gly 270 aat Asn aac Asn	Asp gtc Val ccg Pro	Ser acc Thr gac Asp	atc lle aat Asn 305	ggc Gly 290 tcc Ser	1577 <sup>2</sup> 1625
40	gg Gi; 27: acc Thi aig	a Val 260 t gac y Asp c aag Lys s agc Ser	ggt Gly tac Tyr gga Gly	ctg Leu gat Asp ctg Leu 310	Ctc Leu cag Gln 295 gat Asp	gcc Ala 280 ccg Pro	Thr 265 gcc Ala ggt Gly gac	Leu atc Ile ctg Leu gtc	Thr gaa Glu gga Gly gcg Ala (	aat Asn ctg Leu 300 cag	ggc Gly 285 cgt Arg tac	Gly 270 aat Asn aac Asn gtg Val	Asp gic Val ccg Pro gic Val	Ser acc Thr gac Asp aac Asn 320	atc Ile dat Asn 305 tcc Ser	ggc Gly 290 tcc Ser atc	1577 1625 1673
40	gg Gly 275 acc Thi atg Met	a Val 260 t gac y Asp c aag Lys s agc Ser gat	ggt Gly tac Tyr gga Gly	ctg Leu gat Asp ctg Leu 310 aac	Ctc Leu cag Gln 295 gat Asp	gcc Ala 280 ccg Pro gtc :	Thr 265 gcc Ala ggt Gly gac Asp	atc Ile ctg Leu gtc Val	Thr gaa Glu gga Gly gcg Ala 315 ccc	aat Asn ctg Leu 300 cag Gln	Cys ggc Gly 285 cgt Arg tac Tyr	Gly 270 aat Asn aac Asn gtg Val	Asp gtc Val ccg Pro glc Val	Ser acc Thr gac Asp aac Asn 320 cgc	atc Ile aat Asn 305 tcc Ser	ggc Gly 290 tcc Ser atc	1577 1625 1673
40 45	gg Gly 275 acc Thi atg Met	a Val 260 t gac y Asp c aag Lys s agc Ser	ggt Gly tac Tyr gga Gly gac Asp	ctg Leu gat Asp ctg Leu 310 aac Asn	Ctc Leu cag Gln 295 gat Asp	gcc Ala 280 ccg Pro gtc :	Thr 265 gcc Ala ggt Gly gac Asp	atc Ile ctg Leu gtc Val	Thr gaa Glu gga Gly gcg Ala 315 ccc	aat Asn ctg Leu 300 cag Gln	Cys ggc Gly 285 cgt Arg tac Tyr	Gly 270 aat Asn aac Asn gtg Val	Asp gtc Val ccg Pro glc Val	Ser acc Thr gac Asp aac Asn 320 cgc	atc Ile aat Asn 305 tcc Ser	ggc Gly 290 tcc Ser atc	1577 <sup>2</sup> 1625
40	gg Gly 273 acc Thi atg Met	a Val 260 t gac y Asp c aag Lys g agc Ser gat Asp	ggt Gly tac Tyr gga Gly gac Asp 325	ctg Leu gat Asp ctg Leu 310 aac Asn	Ctc Leu cag Gln 295 gal Asp	gcc Ala 280 ccg Pro gtc Yal tgg	Thr 265 gcc Ala ggl Gly ggc ygac ygac ygac ygac ygac ygac	Leu atc Ile ctg tyal tyal tyal is saac talis is saac tyal	Thr gaa Glu gga Gly gcg Ala Gly	aat Asn ctg Leu 300 cag Gln	Cys ggc Gly 285 cgt Arg tac Tyr	Gly 270 aat Asn aac Asn gtg Val	Asp gic Val ccg Pro gic Val tgg Trp	Ser acc Thr gac Asp aac Asn 320 cgc Arg	alc Ile aat Asn 305 tcc Ser gag Glu	ggc Gly 290 tcc Ser atc Ile	1577 1625 1673 1721
40 45	gg Gly 278 acc Thi atg Met	a Val 260 t gac y Asp c aag Lys s agc Ser gat Asp	ggt Gly tac Tyr gga Gly gac Asp 325 gcc	ctg Leu gat Asp ctg Leu 310 aac Asn	Ctc Leu cag Gln 295 gal Asp	gcc Ala 280 ccg Pro glc Val	Thr 265 gcc Ala ggt Gly gac Hasp	Leu atc Ile ctg Leu gtc Val ata	Thr gaa Glu gga Gly gcg Ala ccc Pro	Alaaat Asn ctg Leu 3300 cag Gln acc Thr	Cys ggc Gly 285 cgt Arg tac Tyr gtg Val	Gly 270 aat Asn aac Asn gtg Val gaa Glu	Asp gic Val ccg Pro gic Val igg Trp 335 gag	Ser acc Thr gac Asp aac Asn 320 cgc Arg	atc Ile aat Asn 305 tcc Ser gag Glu	ggc Gly 290 tcc Ser atc Ile	1577 1625 1673 1721
40 45	gg Gly 278 acc Thi atg Met	a Val 260 t gac y Asp c aag Lys s agc Ser gat Asp	ggt Gly tac Tyr gga Gly gac Asp 325 gcc	ctg Leu gat Asp ctg Leu 310 aac Asn	Ctc Leu cag Gln 295 gal Asp	gcc Ala 280 ccg Pro glc Val	Thr 265 gcc Ala ggt Gly gac Hasp	Leu atc Ile ctg Leu gtc Val ata	Thr gaa Glu gga Gly gcg Ala ccc Pro	Alaaat Asn ctg Leu 3300 cag Gln acc Thr	Cys ggc Gly 285 cgt Arg tac Tyr gtg Val	Gly 270 aat Asn aac Asn gtg Val gaa Glu	Asp gic Val ccg Pro gic Val igg Trp 335 gag	Ser acc Thr gac Asp aac Asn 320 cgc Arg	atc Ile aat Asn 305 tcc Ser gag Glu	ggc Gly 290 tcc Ser atc Ile	1577 1625 1673 1721
40 45 50	gg Gly 278 acc Thi atg Met	a Val 260 t gac y Asp c aag Lys s agc Ser gat Asp	ggt Gly tac Tyr gga Gly gac Asp 325 gcc	ctg Leu gat Asp ctg Leu 310 aac Asn	Ctc Leu cag Gln 295 gal Asp	gcc Ala 280 ccg Pro gtc Yal Trp gag a Glu 1	Thr 265 gcc Ala ggt Gly gac Hasp	Leu atc Ile ctg Leu gtc Val ata	Thr gaa Glu gga Gly gcg Ala ccc Pro	Alaaat Asn ctg Leu 3300 cag Gln acc Thr	Cys ggc Gly 285 cgt Arg tac Tyr gtg Val	Gly 270 aat Asn aac Asn gtg Val gaa Glu	Asp gic Val ccg Pro gic Val igg Trp 335 gag	Ser acc Thr gac Asp aac Asn 320 cgc Arg	atc Ile aat Asn 305 tcc Ser gag Glu	ggc Gly 290 tcc Ser atc Ile	1577 1625 1673 1721
40 45	gg Gly 273 acc Thi atg Met gcc Ala	a Val 260 t gac y Asp c aag Lys s agc Ser gat Asp tcc Ser 340	ggt Gly tac Tyr gga Gly gac Asp 325 gcc Ala	ctg Leu gat Asp ctg Leu 310 aac Asn	ctc Leu cag Gln 295 gal Asp	gcc Ala 280 ccg Pro gtc Yal tgg gag Glu 3	Thr 265 gcc Ala ggt Gly gac Asp Asp hr L 445	atc Ile  ctg  ctg  val  dis I  cac  cac  cac  cac  cac  cac  cac  c	Thr gaa Glu gga Gly gcg Ala 315 ccc	aat aat Asn ctg Leu 300 cag Gln acc Gln	Cys ggc Gly 285 cgt Arg tac Tyr gtg Val	Gly 270 aat Asn aac Asn gtg Val gaa Glu ggt Gly (350	Asp gic Val ccg Pro gic Val tgg Trp 335 gag Glu	Ser acc Thr gac Asp aac Asn 320 cgc Arg gig	Glu atc Ile aat Asn 305 tcc Ser gag Glu gat Asp	ggc Gly 290 tcc Ser atc Ile	1577 1625 1673 1721

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5	Leu (	Glu Arg	Met Ty 260	r Ala	Asp	Gly	Ser. 265	Phe	Gln	Arg	Phe	Leu 270	Thr	Glu
	Asn L	eu Gly. 275	Glu As	p Ser	Gln	Val 280	Val	Gln	Glu	Gly	Thr 285	Pro	Gly/	Asp
10		Ser Phe 190	Leu As	p Glu		,1								
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35	Leu T	hr Leu	Ala GI		Asp	Ser	Ser	Thr 90	Phe	Leu	Ala	Asp	As n 95	Asn
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40	Ala G	lu Ser 115	Leu Ar	g:Ser		11e 120	Asn	Thr	Val			Gly	Gln	.Ala ¹
,		la Ala 30	Arg Se	r Leu	Gly 135	Leu	Gly	Phe	Ser	Asp 140	Ile	Phe	Arg	Ser
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	inr L	eu lle	Ala Lei		Lys	Asn	lhr	1hr 170	He	Ala	Ser	Val	11e 175	Gly
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Pro Gly Pro Ser Phe

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	gig	100	arg	ggc	Lou	ERR	Dea	aig	Acn	Ala	Ila	Tur	Cln	Ala	Ara	Dhe	1140	
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	~~ 1	010			0.00	act	aca	ctg	320	220	rto	gac		ctc	3 C C	ttc	1290	
35								Leu										
	GIY	265	116	1112	Oth	VIG	270		ASII	Non.	LCU	275		DCu	1,111	I n c		
			220	100	320	cto		cgt	ctt	ga f			etc	CPC	ggi	aac	1338	
10								Arg										
40	280	110	,A311	C)3	, ASII	285			bea	7.50	290		, 4.		0,,	295	• •	
	,	220	aic	atr	cag			gag	i. Lece	110			eet	ecc gcc	ggr	1.	1386	
t								Glu										
45	1111	Lys	116	116	300		, LCu		501	305				777.0	310	1.6	,	
43	icc	atr	atc	220			taa	ggc	røt			gal	gaa	cia	. '	gag	1434	
								Gly										
	261	, ,		315	+α:1	110		01,		0.4	11,5	110 P	0.0	325				
50	220	G a C			aat	or 1	.c.11	otr			ato	aac	aac			σac.	1482	
. ·	luc	Sac	Cln	5at Acr	61 v	gυ. Δŀs	۱۱۱) ۱۱م (	Val	Gin	Val	Med	Acn	Asn	Thr	Ser	Asn		
	r A 2	vsh	330		UIY	N 1 a	שבע	335			me t	11511	340	1 11 1	501	215 p.	•	
ر نیا <sup>ن</sup> ہے'۔ استان میں	a cat	. (7.2. )				ماسان	a a.n				<u>o.</u> a.1.	gr.r		a.t.c	c a.t	_02O	1-530	
55																		
33	$\sigma$ $\Gamma$ $\gamma$	ASP	jyΓ	GIT	. inr	rne	LyS	Ala	nsn	voh	UIY	vì q	1 y 1	. 441	LVIB	Olu		

		,	345			٠.		350			•		355						
		cac			ggc	cgt	gac			acc	ctc	aag		gtc	gag	gac	atg	1578	٠
_																	Met		
5		360					365	•			. ,	370					375		
			gac	gag	gag			aag	ctg	ccc	cgt		ggc	cat	gać	tac		1626	
			Asp																
10						380		_,_			385					390			
70		aag	gtc	tac			tac	aag	cgt	gcg		gag	acc	aag	gac		ccg	1674	
			Val																
		2,0		.,.	395		- , -	-,-		400	,				405				
15		acc	gtc	ait		gcc	cat	acc	atc		ggc	tac	ggc	ctg		cac	aac	1722	
			Val																
			,	410			,		415	•				420-		. :			
		ttc	gag	ggc	cgc	aac	gcg	acc	cac	cag	atg	aag	aag	ctg	acc	ctg	gat	1770	
20			Glu		-														
			425				•	430	. ••		. :		435						
		gac	ctg	aag	ctg	iic	cgl	gac	aag	cag	ggt	ctg	ccc	atc	acc	gat	gag	1818	
			Leu																
25		440			٠,٠	å,	445	1, 1				450				¥1. 1	455	·	
		gag	ctg	gag	aag	gat	ccc	tac	ctg	cci	ccg	tac	tac	cac	ccg	ggt	gag	1866	
		Glu	Leu	Glu	Lys	Asp	Pro	Tyr	Leu	Pro	Pro	Туг	Tyr	His	${\tt Pro}$	Gly	Glu		
				٠		460		٠.		,	465	7 × •	. ••			470			
30		gac	gca	ccg	gag	atc	aag	tac	alg	aag	gag	cgl	cgc	cag	gcg	ctc	ggt	1914	,
		Asp	Ala	Pro	Glu	lle	Lys	Tyr	Met	Lys	Glu	Arg	Arg	Glin	Ala	Leu	Gly		
					475	•	٠.		100	480	•	• •		:	485	1	1.4		
			ttc															1962	
35	•	Gly	Phe		Pro	Glu	Arg	Arg		Lys	Tyr	Glu	Pro		Gln	Val	Pro	•	
				490	•			•	495			·		500		•			
																		2010	
		Рго	Leu	-	Lys	Leu	Arg		Val	Arg					Lys	Gln	Gln		;
40			505				,	510				. :-	515			• •	•		
			gcc															2058	
			Ala							_									
45		520																0100	
43			aag															2106	
		Asp	Lys	Asn	Leu					vai			Tie.	Pro	Asp.		Ala	•	
				11.	•					4.4	545					550		9154	
50			acc															2154	
		Arg	Thr.	rne															
•				4	555										565			220	
			cac															2202	
55		rro	His																
	٠.			510	ì,		٠		575			:	. 5.	580.					

entra a

			•														
	tac	cgl	gag	gcc	aag	gac	ggc	cag	alc	ctg	cat	gag	ggc	atc	aac		2250
<u> </u>	Туг	Arg	Glu	Ala	Lys	Asp	Gly	GIn	11e	Leu	His	Giu	Gly	i i e	Asn	Giu	,
		585		٠,٠			590		٠.		***	595	**	•	•. •	•	5
5	gcc	ggt	tcc	glg	gca	lcg	ttt	atc	gcc	gcc	gga	acc	tcc	lac	gcc	acc	2298
	Ala	Glv	Ser	Val	Ala	Ser	Phe	lle	Ala	Ala	Gly	Thr	Ser	Туг	Ala,	Thr	
	600		• • •			605				, .	610	•	•	•	. 15	615	
	cat	ggr	929	gcc	alg		ccg	cig	tac	aic	ttc	tac	tcg	atg	ttc	ggc	2346
10	His	Clv	Glu	Ala	Met	He	Pro	Leu	Tyr	He	Phe	Tyr	Ser	Met	Phe	Gly	
	1113	0.,	0.0		620				- •.	625				* .	630		18 mg
	tto	Lag.	רסר	acc		gac	ggc	atc	igg	gcc	gca	gcc	gac-	cag	atg	acg	2394
	Phe	Clin	Aro	Thr	Glv.	Asp	Gly	He	Trp	Ala	Ala	Ala	Asp	Gln	Met	Thr	
15	inc	0111	Wie	635	<b>.</b>				640			4		645			3 3 4 3
	cat	aat	ttc		rto	ggc.	gcc	acc			cgc	acc	acc	cig	acc'	ggt	2442
•	· Ara	Clv	Dhe	Len	Len	Glv	Ala	Thr	Ala	Glv	Arg	Thr	Thr	Leu	Thr	Gly	
	VIE	GIY	650		Deu	01,		655					660				
20	727	aac	CIC	ráo	Cac	ato	gal			tcc	ccg	atc	ctg	gcc	tcc	acc	2490
	Clu	Clu	Lau	Gin	His	Met	Asp	Glv	His	Ser	Рго	lle	Leu	Ala	Ser	Thr	
	Glu		. ; .				670						, ,			. 4.	
	220	000	aat	ala									tac	gag	atc	gcg	2538
25	Acn	Dro	Clu	Val	Glu	Thr	Tvr	Asp	Pro	Ala	Phe	Ser	Туг	Glu	He	Ala	
	680		013	101		685		,,,,,			690		- •			695	
			atr	Cac				gac	CEC	atg			ccg	ggc	aag	ggt	2586
	Uic	LIE	Val	Hic	Aro	Glv	lle	Asp	Arg	Met	Tvr	Glv	Pro	Gly	Lys	Gly.	
30	шэ	, pcu	741	1113	700				,	705		7.				4. A.	
	ra o	221	ote	atc			o to	acc	alc			gag	cca	acc	ccg	cag	2634
	Clu	Acn	Val	ile	Tyr	Tvr	Len	Thr	11e	Tvr	Asn	Glu	Pro	Thr	Pro	Gln	•
25	Viu	. ASII		71.5		1 3 1	500	• • • • • • • • • • • • • • • • • • • •	720					725		·: •	. 7.
35	cca	art	σασ			σat	ctg	gac			ggc	cig	cac	aag	ggc	atc	2682
	Drn	Ala	Clu	Pro	Clu	Asn	Leu	Asp	Val	Glu	Gly	Leu	His	Lys	Gly	He	
	110	, Ala	730		014	110 p	,	735					740				
40	tac	cic			220	gcc	gcc	,		gag	ggc	cai	gag	gcc	tcg	alc	2730
40	Tur	len	τυυ Τυτ	Asn	Lvc	Àla	Ala	Glu	Glv	Glu	Glv	His	Giu	Ala	Ser	He	
*	191	745		7150			750								,		•
	ctg			990										cgt	gac	aic	2778
45	len	Ala	Ser	Glv	lle	Glv	Met	Gla	Tro	Ala	Leu	Arg	Ala	Arg	Asp	lle	
	760		. 501	013	110						770		٠.		·	775	
			σαο		tac								tcc	gcc	acc	tcg	2826
	Tou	Ala	Clu	, gui	Tur	Clv	lle	Arg	Ala	Asn	. He	Phe	Ser	Ala	Thr	Ser	
50	ren	nia	. 010	nsp	780					785	,		,		790		
, 33	1.00	roman	, (7)				סימרי	gøt	gcr			aan	cle			clg	2874
	rgg T	. Big	. Li	, נוצ יומ!	, <u>δ</u> ιί	. 05°	, bac	Clu	A l'a	i Are	: Are	Asn	Len	Glu	Ala	Leu	. 1 5 T
	110	, tal	UIU		ліа			. UIJ	800	)				805	- ناماند		
55				טפן זה'ה	· a.c.	, ,	ote	. gg1	. 72	י פרי	a ttir	gte	acc	acc	CAS	z ctg	2922
55	cgc	aac	, CCE	5 66 L	Pre	, 5a	. 51	- 55	P 0 6				,				- <b></b>

,	Arg Asn Pro Gly Ala Asp Val Gly Glu Ala Phe Val Thr Thr Gln Leu 810 815 820	• ,
	•	2970 ·
5	Lys Lys Gly Ser Gly Pro Tyr Val Ala Val Ser Asp Phe Ala Thr Asp	
	825 830 835	,
		3018
•	Leu Pro Asn Gln Ile Arg Glu Trp Val Pro Gly Asp Tyr Ile Val Leu	3018
10	840 845 850 855	
		2066
•		3066
	Gly Ala Asp Gly Phe Gly Phe Ser Asp Thr Arg Pro Ala Ala Arg Arg 860 865 870	
15		0114
		3114
	Tyr Phe Asn Ile Asp Ala Glu Ser Ile Val Val Ala Val Leu Arg Gly	
•	875 880 885	0.00
20		3162
	Leu Val Arg Glu Gly Val Ile Asp Ala Ser Val Ala Ala His Ala Ala	
	890 895 900	0010
		3210
25	Glu Lys Tyr Lys Leu Ser Asp Pro Thr Ala Pro Gln Val Asp Pro Asp	
	905 910 915	0.000
		3262
	Ala Pro Ile Glu	
30	920	·
	aigatgaggg gggcggggt gigcicgiti acggcgggia caggggggia icagcccagc	
	ategeettat eggagagest egegeeettg atetiggega atteetgeag eagateeege	
	acggigagel icigeticae cicigegeig geeteataga egateegiee elegigeate	
35	algatgaggc ggttacccag gcggatagcc tgttccatgt tgtgggtgac catgagggtg	
	gicagitige egicelegae galeticieg gicagggigg igaecagite ggetegeigg	
	ggglccaggg cggcggtgtg ttcgtcgaga agcatg	3598
	Z010\ 00	
40	⟨210⟩ 22	
	<211> 923	
	<212> PRT	
	<pre>&lt;213&gt; Corynebacterium thermoaminogenes</pre>	
45		
	<400> 22	
	Met Ala Asp Gln Ala Lys Leu Gly Gly Lys Pro Thr Asp Asp Thr Asn	
	1 10 15	
50	Phe Ala Met Ile Arg Asp Gly Val Ala Ser Tyr Leu Asn Asp Ser Asp	
	20 25 30	:
	Pro Glu Glu Thr Lys Glu Trp Met Asp Ser Leu Asp Gly Leu Leu Gln	•
	35 40 45	
55	Asp Ser Ser Pro Glu Arg Ala Arg Tyr Leu Met Leu Arg Leu Leu Glu	

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	.*	· 50					55					<b>60</b> .			1		
<del> </del>	Are	Ala	Ser	Ala	Lys	Arg	Val	Pro	Leu	Pro-	Pro	Met	Th r	Ser-	-Th:r-	-Asp-	
	65	,				70		-			75	-			·.	80	
5	יעד	Val	Asn	Thr	lle	Pro	Thr	Ser	Met	Glu	Pro	Asp	Phe	Pro	Gly	Asp	*
				• • • • •	85					. 90					95	•	
	Gli	ı Glu	Met	Glu	Lvs.	Arg	Туг	Arg	Arg	Trp	Met	Arg	Trp	Asn	Ala	Ala	
				100					105	٠.	:-			110		• • •	
10	114	e Met	Va l	His	Arg	Ala	Gln	Arg	Pro	Gly	He	Gly	Val	Gly	Gly	His	
e* ,		11101	115	÷ .			,	120	•				125				
	114	e Ser	Thr	Tvr	Ala	Glv	Ala	Ala	Pro	Leu	Tyr	Glu	Val	Gly	Phe	Asn	
		. 130					135					140				* .	
15	His	s Phe	Phe	Arg	Gly	Lys	Asp	His	Pro-	GIY	Gly	Gly	Asp	Gln	Val	Phe	
	1:4	;	٠.		•	150		٠.			155		,			160	
	Ph	Gln	Glv	His	Ala	Ser	Рго	Gly	Met	Tyr	Ala	Arg	Ala	Phe	Leu	Glu	
20					165					170				.:	175		
20	Gly	y Arg	Leu	Thr	Glu	Ser	Asp	Leu	Asp	Sèr	Phe-	Arg	Gln	Glu	Val	Ser.	
•				180					185	•				190		:	
	Tv	r Glu	Gly	Glv	Gly	Ile	Рго	Ser	Tyr	Pro	His	Pro	His	Gly	Met	Pro	٠
25		٠.	195					200					205				٠.
	Ası	p Phe	Trp	Glu	Phe	Pro	Thr	Val	Ser	Met	Gly	Leu	Gly	Pro	Met	Asp	
		210					215			•		220					
	Al	a Ile	Tyr	Gln	Ala	Arg	Phe	Asn	Arg	Tyr	Leu	His	Asn	Arg	Gły	He	
30	2.2	5				230					235		: :			240	
	Ly	s Asp	: Thr	Ser	Glu	Gln	His	Val	Trp	Ala	Phe	Leu	Gly	Asp	Gly	Glu	1
			-		245	1				250		·. ·		•	255	in the	
	Me	t Asp	Glu	Pro	Glu	Ser	Arg	Gly	Leu	lle	His	Gln	Ala	Ala	Leu	Asn	
<i>35</i>				260			*		265	• .						_	
	As	n Leu	ı Asp	Asn	Leu	Thr	Phe	[Val	Ile	Asn	Cys	Asn	Leu	Gln	Arg	Leu	
1		٠.	275														
*	As	p Gly	Pro	Val	Arg	Gly			Lys	He	lle	Gln	Glu	Leu	Glu	Ser	
40		290			ŧ		295				:	300			,		
	Ph	e Phe	e Arg	Gly	Ala	Gly	Trp	Ser	Val	He	Lys	Vai	He	Trp	619	Arg	
	30	5		•		310					315	., .				320	
	_ <b>G</b> 1	n Lli	) Asp	Glu	Leu	Leu	Glu	Lys	ASP	) Gin	ASP	Gly	Ala	Leu	vai	GIU	
45		,								330			ъ.		335		
	Va	Me	Asn	Asn	Thr	Ser	Asp	Gly	ASP	Туг	Gin	Thr	Phe	Lys	Ala	AST	
	•	`		340			٠٠ ٠.	٠.	. 345		0.1			350		<b>T</b> 1	
	As	p Gly	, Ala	Tyr	Val	Arg	Glu	His	Phe	? Phe	e Giz	Arg	ASP	Pro	Arg	Inr	
50			355	j. :	. :			360	) : 		•		ანნ . უ	) 	• • • • • • • • • • • • • • • • • • •	. D-0	
	Le	u Lys	Leu	. Val	Glu	Asp	Met	Thi	r Ast	) GIL	ı GI	1116	: ILD	LYS	Let	. rro	
		370	, (	•••	<b>1</b>		375	)	•		', ·	38l	<i>)</i> . Τ	. 1	, , A	·	
	Ar	g Gly	y Gl-y	/- H.i.s	- Asr	)Ty.i	: Arg	g Ly:	s_Va	l lyı	LAL.	1. A.I.S	і іуг	LYS	AT8	AND	<u>.</u>
55	38	5		.•		390	} .		, .	•	39	· .			*. •	400	,
			*														

	Leu	Glu	Thr	Lys	As p 405				Val							
5	Gly	Tyr	Gly		Gly	His	Asņ	Phe		Gly	Arg	Asn	Ala	Thr	His	
				Leu	Thr	Leu	Asp	Asp 440	Leu	Lys	Leu	Phe	Arg 445	Asp	Lys	
10	Gly	Leu 450	Pro						Leu				Pro	Ţyr	Leu	Pro
	465		Туг	•		470				٠.	475				٠.	480
15			Arg		485	•				490			٠.		495	
				500					505					510		
20								520				٠	525			
		530	Lys			1	535					540		, ,		
25	545		lle Leu			550				٠.	555					560
30			Asp		565				. •	570		٠.		, •	575	
				580	•			,	585					590		
<i>35</i>								600					605	•		
-		610					615					620		,		
40	625					630	. :				635	• • •				640
	Gly	Arg	Thr	Thr	645 Leu	Thr	Gly	Glu	Gly	Leu	Gln	His	Met	qzA	Gly	His
45			He	Leu	Ala	Ser	Thr	Asn	Pro	Gly	Val	Glu	Thr	Туг	Asp	Pro
	Ala		Ser	Tyr	G l.u	He	Ala	His	Leu	Val	His	Arg	Gly	He	Asp	Arg
50			Gly		Gly-	Lys	Gly	Glu	As.n	Val	He					
	705 Tyr		Glu	Pro	Thr	Pro	Gln	Pro		Glu						
55	Glu	Gly	Leu						Leu						735 Glu	Gly

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	2 1 to 1	. 7	740			. 745	•	· .	• • •		750			•
	Glu Gly	His (	Glu Ala	Serl	le Le	u Ala	Ser-	G-1-y	i-lie-	GI y÷	Met-	G-l-n	T-r-p	
		755			76	0				105		: .		
	Ala Leu	Arg	Аја Аго	Asp · l	lle Le	u Ala	Glu	Asp	Tyr	Gly	Ile.	Arg	Ala	
	770	١			775	•			780	200	7 × ×			
	Asn Ile	Phe	Ser Ala	Thr S	Set Tr	p Val	Glu	Leu	Ala	Arg	Asp	Gly	Ala	
	705			790				795	~ , '	1.			800	
0 · , . , . ,	Arg Arg	γ Acn l	len Glu	Alal	Leu Ar	g Asn	Pro	Gly	Ala	Asp	Val	Gly	Glu	
•	Wie wie	, 113·11	805				810	•				815		April 18 Comment
	Ala Phe	Val.	The The	Gln	Leu Ly	s Lys	Gly	Ser	Gly	Pro:	Туг	Val	Ala	
	1,		820		2.5	825		•			830			
5	Val Sei	- Asn	Phe Ala	Thr	Asp Le	eu Pro	Asn	Gln	lle.	Arg	Glu	Trp	Val	
	•	835			84	10	1.2			845			: -	
•	Pro Gly	a Asn	Tyr 11e	Val	Leu G	y Ala	Asp	Gly	Phe	Gly	Phe:	Ser	Asp	
	250	<b>)</b>			855				860	200			٠.	-
20	Thr Arg	o o Pro	Ala Ala	Arg	Arg T	yr Phe	Asn	He	Asp	Ala	Glu	Ser	He	
	OCE			ደ70		•		875					000	
	Val Va	1 Ala	Val Lei	ı Arg	Gly L	eu Val	Arg	Glu	Gly	Val.	Ile	Asp	Ala	
			881	<b>5</b> .			890	. * *		1		039	٠.	
25	Ser Va	1 Ala	Ala Hi	s Ala	Ala G	lu Lys	Týr	Lys.	Leu	Ser.	Asp	Pro	Thr	
	501 14		900			905	<b>;</b> • •			•	910			
	Ala Pr	o Gln	Val As	Pro	Asp A	la Pro	1le	Glu						
20 /		915			-9	20				••				· i
30 /											,	;. :		•
	<210>	23		; r · · ·						¥ ·	• •		* .	j j
	<211>		•				1							
35	<212>				•							· .		
			ebacter	ium, th	nermoa	minog	enes		٠.					
	•					1	. *							•
	⟨220⟩			• •/		• 4		, .		٠,				٠,
40	<221>	CDS				-			s in			· . :		
	(222)	(319).	(3735	)				. •				3		
	•	· · · ·	٠.,	•			100		· •		. ,			,
100	<b>&lt;400&gt;</b>	23	*		٠.			•		• • • •				
45 (	giccii	itig	caaatto	tgc a	aagig	ggia g	agglo	cagat	gtc	agca	iggl	cggt	ccgal	1 60
,	101018	ogaa :	agtggag	ccg t	tgggg	gcaa c	attaa	accii	l ccc	CCIE	ggga	igia	gciaa	a 120
	ragraa	1000	ggtctcs	ggc g	ggggg	call c	tttt	cacge	g caa	iggig	gglg	aaaı	recge	a lou-
	ggicac	dece (	cggccgg	cgg t	agaga.	acgg a	gcgaa	aaace	g gaa	lagea	aala	cgra	giii	C 240
50	cggact	ggcc	gitacga	itgt t	ctgaa	gagl g	actg	ccato	c acc	caa	cagg	cigg	giccic.	g 300
	legaaa	iggaa	caaaaa	t gtg	gtt	aca àc	a aca	a cco	ctcc	ac	g Cli	g ccg	ggcg	351
•		-	,	Val	Val	Thr Th	r Th	r Pro	o Ser	Th	r Lei	rre	Ala.	
				1			: .	5				10	) 	
55	tic as	a aag	atc c	ig gig	gcc	aac cg	a gg	t ga	a ato	gc;	g gt	g cg	a gca	3,99.
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	Phe	Lys	Lys	He 15		Val	Ala	Asn	Arg 20	Gly	Glu	He	Ala	Va l 25	Arg	Ala	. :	
5		cgc															447	
	Phe	Arg	Ala 30		Tyr	Glu	Thr	Gly 35	Ala	Ala	Thr	· Val	Ala 40		Tyr	Pro	•	
	cgg	gag			ggc	icc	ttc		cgc	tcc	ttc	gcc	tcc	gag	gcg	gig	495	
10	Arg	Glu		Arg	Gly	Ser		His	Arg	Ser	Phe		Ser	Glu	Ala	Val		
		45 alc			<b>~~~</b>	aac	50		atc	220	aca	- 55	ctc	σa t	ati	an t	543	
		lle															343	
15	60		0.,	• • • •		65		•••			.70			,		75		
		alc															-5,91	•
	Glu	lle	He	Asn		Ala	Lys	Lys	Val	Lys 85	Ala	Asp	Ala	Val		Pro		
20	σόσ	tat	ggi	ttc	80 ctt	tcg	gaa	aat	800		ctc	aca	cel	gaa	90 ter	ere.	639	
		Tyr				_	- ,					-	-	_	_			
				95					100					105				
2.5																	687	
25	Glu	Asn	61y 110	116	ınr	rne	116	115	Pro	inr	PTO	GIU	120		ASD	Leu		_
	acg	ggc		aag	tcc	aag	gct			gcc	gcg	aag			ggg	clg	735	
	Thr	Gly	Asp	Lys	Ser	Lys		Val	Ser	Ala	Ala		Lys	Ala	Gly	Leu		
30		125					130					135						٠.
		gig Val		-													783	
	140		LCu	A10		145		110	501		150	110	пар	Olu	110	155		
35		agt	gcc	gag	ggg	cag	acc	tac	ccg	atc	ttc	gtc	aag	gcc	glc	gca	831	
	Lys	Ser	Ala	Glu		Gln	Thr	Туг			Phe	Val	Lys	Ala		Ala		
	ggt	ggt			160	aat	a 1 <del>a</del>	caa	-	165	<b>72.</b> 7			an a	170	e ta	879	
40		Gly							•								013	٠.'
		,	,	175	0				180					185			•	
		gag										•					927	
45	Arg	Glu		Ala	Arg	Glu	Ala	Ser 195			Ala	Glu	Ala 200	Ala	Phe	Gly		
	gar.	gga.	190	alc.	lac	ø f <sup>i</sup> c	gaa		gcc		alc	ааа		cap	cac	atc.	975	
		Gly																
	•	205	•				210	٠.			•	215	. •					
50		gtg															1023	,
	Glu 220	Val	GIn	He	Leu	Gly 225	ASD	HIS	Th r	Gly,	Asp 230	Val	He	HIS	Leu	Tyr 235	•	
		cgc	gac	igi	tcc		cag	cgc	CEC	cac		aag	gic	gtġ	gag		1071	
55		Arg																•

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			4	•	240		-			245		•	•				
	gca	cct	gcc	cag	cac	ctc	gac.	ccg	gag	ctg	cgc	gac	cgc	atc	tgt	gcc	1119
5	Ala	Pro	Ala	Gln	His	Leu	Asp	Pro	Glu	Leu	Arg	Asp	Arg	He	Cy s	Ala	
				255		,	• :	. :	260 <sup>-</sup>	:	•	-		265			
	gat	gcc	gtg	aag	itc	tgc	aaa	tcc	atc	gga	tac	cag	ggc	gcc	ggc	acc	1167
	Asp	Ala	Val	Lys	Phe	Cys	Lys	Ser	Ile	Gly	Tyr	Gln	Gly	Ala	Gly	Thr	
10			270	٠,		٠.	. *	275			* * *		280				
	gtg	gag	ttc	ctc	gtc	gac	gaġ	gcg	gġc	aac	cac	glc	ttc	att	gag	atg	1215
	Val	Glu	Phe	Leu	Val	Asp	Glu	Ala	G1y	Asn	His	Val	Phe	He	Glu	Me t	·
		285	· · · · ·				290	: . '				295		۲.			
15	aac	CCC	CEC	atc	cag	glg	gaa	cac	acc	gtg	acc	gag	gag	gtc	acc	tcc	1263
	Asn	Рго	Arg	He	Gln	Vál	Glu	His	Thr	Val	Thr	Glu	Glu	Val	Thr	Ser	ent of the co
	300				¥	305			. <del>-</del> .		310	• _ •				315	
	gtc	gac	ctg	gtc	aag	gcg	cag	alg	cac	ctg	gcc	gcc	gg t	gcc	acc	cig	1311
20	Val	Asp	Leu	Val	Lys	Ala	Gln	Met	His	Leu	Ala	Ala	Gly	Ala-	Inr	Leu	
					320	7	•			325					330		
	aag	gaa	clg	ggc	ctg	acc	cag	gac	aag	atc	acc	acc	cac	ggt	gcc	gcc	1359
	Lys	Glu	Leu	Gly	Leu	·Thr	Gln	Asp	Lys	lle	Thr	Thr	His	Gly	Ala	Ala	
25				335			100	, ; ;	340	٠, ٠		4.5		345	,		
•	ctg	cag	tgc	cgc	atc	acc	acg	gag	gac	ccg	tcc	aac	aac	ttc	cgg	ccc	1407
*	Leu	Gln	Cys	Arg	Ile	Thr	Thr	Glu	Asp	Pro	Ser	Asn	Asn	Phe	Arg	Pro	
	*		350					355		2.5		-	360			٠.	
<i>30</i>	gac	acc	ggt	gtg	atc	acc	gcc	tac	cgc	tcc	ccg	ggt	ggt	gcg	ggt	gtg	1455
	Asp	Thr	Gly	Val	He	Thr	Ala	Tyr	Arg	Ser	Pro	Gly	Gly	Ala	Gly	Val	
	•	365		;			370				•	375				1	1500
	cgt	ctc	gac	ggc	gca	gcc	cag	ctc	ggc	ggc	gag	atc	acc	gca	cat	ttc	1503
<b>35</b>	Arg	Leu	Ásp	Gly	Ala			Leu	Gly	Gly	Glu	lle	Thr	Ala	His	Phe	
	380	) .	÷7.	`:		385					390					395	1551
	gat	tcc	atg	ctg	gic	aag	atg	acc	tgc	cgc	ggt	lcc	gaı	IIC	gag	acc	1551
	Asp	Ser	Met	Leu			Met		Cys	Arg	Gly	Ser	ASP	rne	610	Thr	
40					400	۱ .		. 12		405					410		1599
	gco	gte	tcc	cga	gcc	cag	cgc	gcc	ctg	gcg	gag	; iic	aac	gic	. 100	ggc	1035
	Ala	Val	Ser			Gln	Arg	, Ala	. Leu	Ala	Glu	rne	ASN	Val	Ser	Gly	
45			2.5	415	-			•	420					425			1647
45	gig	ggc	acc	aac	ato	ggo	: 110	ctg	cgt	gcg	g Cla	z cig	cgo	gag	gaa	a gac	1647
	Val	Ala	Thr	Ası	He	Gly	Phe			g Ala	ı Lei	ı Leu	Arg	ָנוּט	GIL	ı Asp	
		•	430	)				435				:	440		٠.		1.005
50	i <b>t t</b> c	aco	aag	gage	g égo	ato	ga	acc	gg	: 110	ato	ggo	100	cac	Cag	g cac	1695
. J <b>ų</b>	Phe			Arg	Arg	g 11,6	Asr	o Thi	Gly	Phe	9 116	e GIV	Sei	HIS	GII	n His	
		445					45(				• •	455	-				1749
	cts	cto	cag	ggc	cca	cca	ggc	gad	ga	l gas	g ca	g ggg	g cgg	g ald	C [ ]	g gaa	1743
<i>55</i>	Let	ı Let	ı Gin	ıAla	Pro			a Asr	ASI	o Gli	ı GH	n GIS	/ AI	3 116	. Lei	u Glu	
- · · ·	460	)	•			46	5:	•		Ś.,	47	υ ''		٠. ٔ		475	

	tac	ctg	gcg	gat	gtc	acc	gtg	aac	aaa	ccc	cac	ggt	gaa	cgc	ссс	gag	1791	
	Tyr	Leu	Ala	Asp		Thr	Vai	(As n	Lys		His	Gly	Glu	Arg	Pro	Glu		
5					480		•			485					490			
																clg	1839	
	Thr	Ala	Arg		He	Glu	Lys	Leu.		Glu	Val	Glu	Asn		Pro	Leu	,	
				495					500					505				
10								ctg									1887	
	Pro	Arg			Arg	ASP	Arg		Lys	Gin	Leu	GIY		GFU	GIY	Phe-		
			510					515	~~~	a t =	~~~	<b>~</b> t ^	520	~~~			. 1005	
		-						ga t Asp									1935	
15	Nid	525	-	Leu	uig	GIU	530	no h	піа	LCu	Ala	535	1111	vsh	1111	1111		
	110			orr.	cac	Cap		ctc	ctø	ac c	acc		ete	רפר	tee	ttc	1983	
		_	_													Phe		
20	540		тэр			545	001	DC u	DC. G	۸ ۵	550					555		į.
			acc	CCG			cgc	gcc	gtc	gca			acc	ссс		ctg	2031	٠.
•								Ala										
				,	560					565					570			
25	clg	tcg	gtg	gag	gċc	tgg	ggc	gg t	gcc	acc	tac	gac	gtg	gcc	atg	cgc	2079	
	Leu	Ser	Val	Glu	Ala	Trp	Gly	Gly	Ala	Thr	Туг	Asp	Val	Ala	Met	Arg	•	
			*.	575					580					585				•
																	2127	
30	Phe	Leu			.Asp	Pro		Ala.		Leu	Asp	Glų		Arg	Glu	Ala		
			590				•	595				:_ 4	600	. ,	• ;		0175	
								atg									2175	•
<i>3</i> 5	Mer	605	ASII	vai	ASII	116	610	Met	Leu	Leu	Alg		Aig	ASII	1111	Val	•	
	aaa		300	cca	tac	ccc		tcg	ata	tar				ala	CaG	020	2223	
																Glu.		
	620	.,.	• • • • •			625					630				,••••	635	,	ż
40		gcc	aag	tcc				atc	ttc			ttc	gac	gcg	clc		2271	•
								He										
					640		· .	•		645					650		•	
•	gac	a t c	tcc	cag	alg	cgc	ccg	gcc	alc	gac	gcc	glc	clg	gag	acc	ggc	2319	
45	Asp	I le	Ser	Gln	Met	Arg	Pro	Ala	He	Asp	Ala	Val	Leu	$G \mid u$	Thr	GI y.	:	
				655		-	· .		660	•				665				
	acc	agt	gll	gcc	gag	gtc	gcc	atg	gcg	tac	lcc	ggt	gac	cig	tcc	aat	2367	
50	Thr	Sei		Ala	Glu	Val	Ala	Met	Ala	Туг					Ser	Asn		
50			670	ě			•	675				٠ •						
								cig						•			2415	
	Pro		Glu	Ly.s	Leu.	Туг		Leu	Asp	Tyr	Tyr		Asn.	Leu	Ala	Glu	÷	
55	0.5.5	685	~ · -				690					695					9.400	
	cag	aic	.g į C	gac	.1 C C	gg (	gca	cac	arç	cig	gcc	aic	aag	gac	alg	gcc	2463	

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, and  $\langle \tau_{\rm s} \rangle = 1/(4)$  , with the

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		Cln	TIA	Val	Asn	Sar.	Clus	Δla	His	He	Leu	Ala	He	Lvs	Asp	Met	Ala		ć
		700	116	V.d.1 ,	vah	261	705	AIG				710-		<del>-,</del> -			-7-1-5		
		770	c t a	eta	12	Cac		σrσ	gcg	bac				acc	gcc	cig	cgc ·	2511	
5		Clu	Lou	Len	Ara	Δτα	Ala	Ala	Ala	Pro.	Lvs	Leu	Val	Thr	Ala	Leu	Arg		
		СТУ	Leu	Leu		720	лга	7110			725					730			
					<b></b>		CCC	σισ	cat	átr			.cac	gac	acc		ggc	2559	
		Cgi.	gaa	Diba	gac	Lau	Dra	Val	Hic	Val	His	Thr	His	Asp	Thr	Ala	Gly		
10		Arg	Glu	rne		Leu	110	141	ŭio	740		• • • • • • • • • • • • • • • • • • • •		,	745				
		4			735		120	ct or	gcc		ac c	aac	ጀርር	ggg	_	gat	gcc	2607	
		ggı	cag	CIG	gcc	acc	Tue	Leg	Ala	Ala	Δla	Acn	Ala	Glv	Ala	Asn	Ala		
		GIY	Gin			THE	1 1 1	Leu	755	νια	NI G	ДЗП	AT G	760	,,, u			. '7.	
15	٠.			750		·	-					200	2 C C		Cao	cca	tro	2655	
		glc	gac	gcc	gcc	CC	gca	Do.	clg	Cor	Cly	The	The	Ser	Cln	Pro	Ser	2000	
		Val		Ala	Ala	Ser	Ala		Leu	361	GIY	1111	775	361	GIII	110	JUL		
			765					770						0.00	<b>410</b>	200	aar	2703	
20		aig	tcc	gct	ctg	gtt	gcc	gcg	tit	gcg	Cac	The	\ ra	\ ra	Acn.	The	Clv	2103	
				Ala	Leu	Val		Ala	Phe	Ala	HIS	700	Arg	AIR	W2D	1 11 1	795		
· · ·		780					785	.*				790						9751	
		CIC	aac	ctg	cag	gcc	gic	tcc	gac	cig	gaa	CCg	tac	t gg	gag	gcg	gic	2751	
25		Leu	Asn	Leu			Val	Ser	Asp	Leu	GIU	ΪL0	INI	110	GIU	Ald	y a 1		
		•				800	· .·				805		·			810		9700	•
		cgc	gga	ctg	tac	ctg	ccg	ttt	gaa	tcc	ggc	acc	ccg	ggc	CCG	acc	gga	2799	
		Arg	Gly	Leu					Glu			Thr	Pro	Gly	PIO	Inr	GIY		
<i>30</i> '		•			815					820		·			825		·	9047	
		cgc	gtt	tac	cgc	cac	gag	ato	ccc	ggc	ggt	cag	cig	lcc	aac	cig	cgt	2847	
		Arg	Val			His	Glu	He		Gly	Gly	Gln	Leu	Ser	Asn	Leu	Arg		
				830			: .		835			,		840			,	0005	
35		gcc	cag	gcc	gtt	gca	ctg	ggt	ctg	gcc	gac	cgc	ttc	gag	CIC	aic	gag	2895	
		Ala	.Gln	Ala	Val	Ala	Leu		Leu	Ala	Asp	Arg	Phe	Glu	Leu	116	GIU		
• •			845					850					855		•			0040	
		gac	tac	tac	gcg	gcc	gtc	aac	gag	atg	ctg	ggt	cgt	ccg	acc	aag	gic	2943	
40 -		Asp	Туг	Туг	Ala	Ala	Val	Asn	Glu	Met	Leu	Gly	Arg	Pro	Thr	Lys	Val		
:		860					865	.:				870			: '		875		
		acc	ccg	100	icc	aag	gti	gto	ggt	gac	ctc	gca	ı.ctg	cac	cto	gio	ggı	2991	
		Thr	Pro	Ser	Ser	Lys	Val	Val	Gly	Asp	Leu	Ala	Leu	His	Leu	Val	Gly	-	•
45						880										890	,		
		gcc	ggt	glg	agc	ccg	gag	ga	litc	gcc	gcc	gat	CCE	cag	aag	, tac	gac	3039	
		Ala	Gly	Val	Ser	Pro	Glu	Asp	) Phe	Ala	Ala	Asp	Pro	Gln	Lуs	Туг	Asp		
٠.	•				895	٠.	a .			900					905			:	
50		atc	C.C.C	gal	tcg	glc	ato	gc	110	cto	cgo	ggo	gaa	clg	ggt	. acc	100.	3087	
	•	He	Pro	Asp	Ser	Va I	He	Ala	a Phe	Leu	Arg	g Gly	Glu	Leu	Gly	Thr	Pro		
				910					915		2			920	(1) - a		: 5.		
	<b></b>	CCC	ggt	ggc	tgg	; 'c'c c	gaa	c.c.8	gclg	-cgc	-acc	-cg	- gc-a	ac-t c	-gag	g-gg	-cgc	31-35	
<i>55</i>		Pro	Glv	Glv	Tro	Pro	Glu	Рг	. Leu	Arg	Thi	. Are	g Ala	a Leu	Gli	ı, Gly	Arg	•	
				3			_			-									

tec cag ggt aag gec eeg etg geg gag ate eeg gag gag eag gee 3183  Ser Gin Gly Lys Ala Pro Leu Ala Glu lie Pro Ala Glu Glu Gin Ala 940 945 950 955  cac eig gat tee gat gat tee geg gag egt ege gge ace et aac ege 3231  His Leu Asp Ser Asp Asp Ser Ala Glu Arg Arg Gly Thr Leu Asn Arg 960 965 970  cig eig tie eeg aag eeg ace gag gag tie eit gag eac egt ege ege 3279  Leu Leu Phe Pro Lys Pro Thr Glu Glu Phe Leu Glu His Arg Arg Arg 975 980  10 10 10 10 10 10 10 10 10 10 10 10 10 1		925 930 935	٠,
Ser Gln Gly Lys Ala Pro Leu Ala Glu Ile Pro Ala Glu Glu Gln Ala 940 940 945 950 cac cig gai ice gai gai ice geg gag cel cec gec acc cit cac cec 3231 His Leu Asp Ser Asp Asp Ser Ala Glu Arg Arg Gly Thr Leu Asn Arg 960 965 970 cig cig iice ceg aag ceg ace gag gag iice cii gag cac cel cec ceg Leu Leu Phe Pro Lys Pro Thr Glu Glu Phe Leu Glu His Arg Arg Arg 975 980 985 15 11c ggc aac ace ice gec cig gai gac cec gag at ite iite tac ggc iig 985 15 11c ggc aac ace ice gec cig gai gac cec gag at ite iite tac ggc iig 990 995 1000 aag gag gga cel gag gag cig aic cea cig ace ggi gli ce ace cec 990 995 1006 1016 1016 1016 1016 1016 1016 101			3183
946 945 950 955 cac cig gai icc gai gai icc gag gai cgc ggc acc cic aac cgc His Leu Asp Ser Asp Asp Ser Ala Giu Arg Arg Giy Thr Leu Asn Arg 960 965 970  cig cig itc ccg aag ccg acc gag gag itc cit gag cac cgt cgc cgc Leu Leu Phe Pro Lys Pro Thr Giu Giu Phe Leu Giu His Arg Arg Arg 975 980 985  15 tic ggc aac acc icc gcc cig gai gac cgc gag itc tit tac ggc itg 976 999  aag gag gag cgt gag gag cig at c cga cgg ag itc tit tac ggc itg 977 1000  aag gag gag cgt gag gag cig at c cga cig acc ggt gig itcc acc ccg 3375  Lys Giu Giy Arg Giu Giu Leu iie Arg Leu Thr Giy Val Ser Thr Pro 1005 1010 1015  alig gig gic cgc cig gai gog gig icc aac gcg gai gac aaa ggc atg Met Val Val Arg Leu Asp Ala Val Ser Giu Pro Asp Asp Lys Giy Met 1020 1025 1030 1035  cgc aac gig gig gic aac gic aac ggc cag at c cgc cga ac aag gig 3471  Arg Ash Val Val Ash Val Ash Giy Gin Iie Arg Pro Iie Lys Val 1040 1045 1050  30 cgc gac cgt icc gig gag icc gic acc gcc acc gcg gag aag gcc gai Arg Asp Arg Ser Val Giu Ser Val Thr Ala Thr Ala Giu Lys Ala Asp 1055 1060 1065  30 cgc aac gac gac gag ggc cal gic gcc gca acc at ic gcc ggi gg gcc 3567  Ala Thr Ash Lys Gly His Val Ala Ala Pro Phe Ala Gly Val Val Thr 1070 1075 1080  31 gig acc gic gcc gag ggi gad gag gcc acc acc acc gcc gcc gcc gig gcc 3615  Val Thr Val Ala Giu Gly Asp Giu Ile Lys Ala Gly Asp Ala Val Ala 1085 1090 1095  at cat it gag gcc at gag gag gcc acc acc acc gcc acc gcc gcc	5	Ser Gin Gly Lys Ala Pro Leu Ala Glu lle Pro Ala Glu Glu Gin Ala	0100
cac cig gai toc gai gai loc gag gag cgi cgc ggc acc cic aac cgc His Leu Asp Ser Asp Asp Ser Ala Glu Arg Arg Gly Thr Leu Ash Arg 960 965 965 970 cig cig iic ccg aag ccg acc gag gag iic cii gag cac cgi cgc cgc Leu Leu Phe Pro Lys Pro Thr Glu Glu Phe Leu Glu His Arg Arg Arg 975 980 985 15 Iic sgc aac acc icc gcc cig gai gac cgc gag iic cii cac ggc iig Phe Gly Ash Thr Ser Ala Leu Asp Asp Arg Glu Phe Phe Tyr Gly Leu 990 995 1000 aag gag gga ggi gag gag cig alc cga cig acc ggi gig icc acc cc g 1005 1010 1005 1010 1005 1005 1000 1005 1000 1005 1000 1005 1006 1006		040	
His Leu Asp Ser Asp Asp Ser Ala Glu Arg Arg Gly Thr Leu Asn Arg 960 965 976 cig cig tic ccg aag ccg acc gag gag tic cit gag cac cgt cgc cgc 3279 Leu Leu Phe Pro Lys Pro Thr Glu Glu Phe Leu Glu His Arg Arg 975 980 985 15 tic ggc aac acc tcc gcc ctg gat gac cgc gag tic tic tac ggc ttg 3327 Phe Gly Asn Thr Ser Ala Leu Asp Asp Arg Glu Phe Phe Tyr Gly Leu 990 995 1000 aag gag gga cgt gag gag ctg atc cga ctg acc ggt gtg tcc acc ccc 3375 Lys Glu Gly Arg Glu Glu Leu He Arg Leu Thr Gly Val Ser Thr Pro 1005 1010 1015 alig glg gic cgc ctg gat gg gg gig tcc gaa ccg gat gac aaa ggc atg 3423 Met Val Val Arg Leu Asp Ala Val Ser Glu Pro Asp Asp Lys Gly Met 1020 1025 1030 1035 cgc aac glg glg glc aac gtc aac ggc cag atc cgc ccg atc aag gtg 3471 Arg Asp Val Val Val Asn Val Asn Gly Gln Hie Arg Pro He Lys Val 1040 1040 1040 1040 1040 1040 1040 104			3231
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	Val Asn Glu Leu Leu Arg Asp Asp Ile Arg Tyr Leu Gly Arg Ile
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5	ctg cac gcc ctg gaa cac gaa ctc agt ctc tcc gac cgg atg aac gtc Leu His Ala Leu Glu His Glu Leu Ser Leu Ser Asp Arg Met Asn Val	972
10	atc agc gat gag ctg cgt gtg ctt gcc gat gcc ggc cag aat gac atg lle Ser Asp Glu Leu Arg Val Leu Ala Asp Ala Gly Gln Asn Asp Met	1020
15	ccc agc cgg git gat gaa ccc tac cgg cgg gcc atc cac ggc atg cgt Pro Ser Arg Val Asp Glu Pro Tyr Arg Arg Ala lle His Gly Met Arg	1068
2 <b>0</b>	ggc cgg aig cig gcc acc acg gcc gcc cig aic ggt gag gag gcg gic Gly Arg Met Leu Ala Thr Thr Ala Ala Leu Ile Gly Glu Glu Ala Val	1116
20	gag ggc acc igg iic aag acc iic acg ccc iai acc gat acc cac gag Glu Gly Thr Trp Phe Lys Thr Phe Thr Pro Tyr Thr Asp Thr His Glu	1164
25	tic aaa cgc gac ctc gat atc gtg gat ggt tcc ctg aga atg tcc cgg Phe Lys Arg Asp Leu Asp Ile Val Asp Gly Ser Leu Arg Met Ser Arg	1212
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35	gac age ite ggg ite aac eie tac iee eig gat eig ege eag aai tee Asp Ser Phe Gly Phe Asn Leu Tyr Ser Leu Asp Leu Arg Gln Asn Ser 400 405 410	1308
40	gac ggt tic gag gat gic cic acc gaa tig tic gcc acc gcc cag acc Asp Gly Phe Glu Asp Val Leu Thr Glu Leu Phe Ala Thr Ala Gln Thr 420 425 430	1356
	gag aag aac tac cgc ggg tig acg gag gcg gag aag cig gac cig cig Glu Lys Asn Tyr Arg Gly Leu Thr Glu Ala Glu Lys Leu Asp Leu Leu 435 440 445	
45	atc cgc gaa ctg agc aca ccc cgc ccg ctc atc ccg cac ggg gac ccg lle Arg Glu Leu Ser Thr Pro Arg Pro Leu Ile Pro His Gly Asp Pro 450 455 460	1452
50	ASP TYP Ser Glu Ala Thr Ash Arg Glu Leu Gly Ile Phe Ser Lys Ala 465 470 475	1500
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	t gg	gtg	ctc	agc	tgg	tcc	cag	icc	cgt	glc	alg	ctg	ccg	ggc	tgg	ttc	2364
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	gcgl	cacc	a t c	ctga	ccgc	agt	cato	tggt	lga	itcig	cal	tgto	gcgc	ic a	acct	catcc	3150
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		Thr	His	Arg 275		•	Glu		Val 280		Lys	Tyr		Val 285	Lys	Gln	Leu
5		His	Ala 290	Leu	Glu	His		Leu 295	Ser	Leu	Ser	Asp	Arg 300	Met	Asn	Val	He
		Ser 305	Asp					Leu	Ala				Gln	Asn			
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5		. ,	Val.	ATO	Val	Thr	Glu	Gln	Gly	Glu	He	Ile.	Ser	Ala	Lys	Tyr	Gly	Asn	
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### <213> Corynebacterium thermoaminogenes

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        Lys Lys Gln Phe Asp Leu Asn Gly Gln Ser Tyr Thr Tyr Tyr Asp Leu
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		ł.	370	1				375	,				380		·	*		
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•	•	385		,			390	,				395			٠	, , , , ,	400	
	•	Pro	Ala	Gly	Asn	Gin	Gly	His	Gly	Leu	Asp	Glu	Ser	Glu	Phe	Asp	Lys	
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										,								
			,			. 42	0			• ;•	42	5		, S. '	:	430	0 .	
		(	Gly		p Va	l Ala	a II	e Ala	a Ala	a II	e Th	r Se	г Су:	s Th	r Ası	n Th	r Se	r Asn
5				•		5			• •	44	0				44			
		ł	,10	ly	r Va	I Me	Le	u Gly	Ala	a Gl	y Lei	u Va	I Ala	a Ly:	S Ly:	s Ala	a IIg	e Glu
		ī	1/ C	45)	ים ים די	ı Ive	Va	l D-,	45;	).' S. Tsu:	- Val	; 1	TL.	460	) - 1 -		<b>.</b>	
			65	U I	y LEI	. град	s ra.	470	) voi	JIY	Y a.	I Ly:	5 1111 171	s sei	Let	J Ala	1 Pro	Gly 480
10			1. 4	Lys	s Val	Val	Thi	Glv	Tvi	Lei	ı Are	e Asi	Sei	, Glv	 Lei	1 . G l <del>1</del>	. Cla	460 Tyr
							485	;				490	) , 1		500		495	, , , ,
		L	eu	Ası	Asp	Leu	Gly	' Phe	Asr	Lei	ı Val	l'Gly	Tyr	Gly	Cys	Thr	Thr	Cys
15						500			• .		505	;			· · :	510	) .	
-		I.	l e	Gly	/ Asn	Ser	Gly	' Рго	Leu	Let	Pro	o Glu	Ille	: Glu	Lys	Ala	Val	Ala
		. Δ	cn	C1.	616 028 -	). 	Lau	Val	Th-	520	) . Vol	T			:525			
20		Л	งท	530	) I Wah	Leu	Leu	, vai	525	261	Yaı	Leu	ser	GIY	Asn	Arg	Asn	Phe
									Leu	Val	Lvs	Ala	Asn	Tvr	i. Ten	Ala	Ser	Pro
		5	45		_		,	550			_,,		555			11.14	501	560
		G	l n	Leu	Val	Val	Ala	Tyr	Ala	Leu	Ala	Gly	Thr	Val	Asp	He	Asp	Leù
25			••			_ ;	565					570			•		575	
•	,	. H:	I S	Asn	Glu	Pro	He	Gly	Lys	Gly	Lys	Asp	Gly	Glu	Asp	Val		Leu
•		· I.v	/S	Asn.	م11	DBU Trn	Pro	900	114	I u e	585	Val			ጥኤ -	590		Ser
30	•				595	110	1,10	,501		600	Olu	141	піа	АЗР	. 605	vai	ASP	261
		<b>V</b> a	d i	Vai													Tyr	Glu
			, !	610		1,1			615				· .	620	• . •		:	
م خ		As	n .	Asn	Glu	Met	Trp	Asn	Glu	lle	Asp	Val	Thr	Asp	Ala	Pro	Leu	Tvr
35	•	62	5 n 1	Dha	100	D = 0	سنا	630	Фъ.	•		•	635	_:	٠.		٠,	640
		۸۵	, q	ne	Asp	110	645	261	Inr	lyr	116	GIN	Asn	Pro	Ser	Phe		
					Ser	Lvs										: Acn	655	Arg
40						660		-	0.,	****	665	oru	110	ric a	L y S	670	ren	MIR
	,	$\Pi$	e N	le i	Gly	Lys	Phe	Gly	Asp	Ser	Val	Thr	Thr	Aso	His	Ile.	Ser	Pro
• •					675	7				680	·	. • .	•		685	$v \cdot v$		•
45	•	. A1	a G	ly	Ala	He	Gly	Lys.	Asp	Thr	Pro	Ala	Gly	Lys	Tyr	Leu	Leu	Asp
		н		90		D = 0								700				
		708	ъл 5	2h	Val	110	116	710 ·	610	rne	AS II	261		Gly	Ser	Arg	Arg	
٠				is	Glu	Val 1	Met	Val	Агр	Glv	Thr	Phe	715	Δen	Ilo	Λ+α·	i Na	720
50					/		725				· · · · ·	730	nı a	A3II	116	AI B	735	
		Asл	G	l n	Leu .	Ala 1	Pro	Gly '	Thr	Glu	Gly	Gly.	Phe	Thr	Thr.	Туг	Tro	Pro
						740		*. **			745					750		
<b>5</b> 5		Thr	G	lu (	Glu	lle l	de t	Pro'	11e	Туг	Asp.	Ala -	Ala	Me i	Arg	Туг	Lys	Glu
					755				2	760	· · .	<i>.</i>			765			

	Asn Gly Thr Gly Leu Ala Val Leu Ala Gly Asn Asp Tyr Gly Met Gly	
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	Ser Ser Arg Asp Trp Ala Ala Lys Gly Thr Asn Leu Leu Gly Val Lys	
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	Thr Val lle Ala Gln Ser Tyr Glu Arg Ile His Arg Ser Asn Leu Val	
	810	
	Met Met Gly Val Leu Pro Leu Gln Phe Lys Gln Gly Glu Ser Ala Asp	-
10	825	
ta iliye Tarihin	Ser Leu Gly Leu Glu Gly Lys Glu Glu Ile Ser Val Asp Ile Asp Glu	, .
	835 840 845	٠.
15.	Asn Val Lys Pro His Asp Leu Val Thr Val His Ala Lys Lys Glu Asn	
	850 855	
	Gly Glu Val Val Asp Phe Glu Ala Met Val Arg Phe Asp Ser Leu Val	
	865 870 875 880 880	
20	Glu Leu Asp Tyr Tyr Arg His Gly Gly Ile Leu Gln Met Val Leu Arg 885 890 895	•
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	Asn Lys Leu Ala Gin	
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	<211> 3006	٠.
	<pre> &lt;212&gt; DNA &lt;213&gt; Corynebacterium thermoaminogenes </pre>	٠.
30.	(21.5). Conynicodo (Crista Chica Escape Constitution Con Constitution	
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	<221> CDS	
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* .	<b>&lt;400&gt; 29</b>	-
mark many	gicgacgacg aacccccac cgccgaacca gccgccgaic iggigiggga gacacccggg 60	
40	therefore tgggtgaaca ggtgccacaa ccccgtccca acaggcacac claccactgg 120-	
	alcorroppy agageageat ggleacaege etgeggegtg ceelgglgaa ggaleaegge lau-	4
	ciggacagat cgcaggiggc alicatgggi tattggaggc agggagiggc calgaggggt 240	
	lgalatogot tocotgaggg tocgoaggog tgcotcacco tgtattottg atagttgaac 300	
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	Met Ala Lys Ile Ile Trp Thr Arg Thr	
14 - 1	1	
	gac gaa gca ccg ctg ctc gcg acc tac tcg ctg aag ccg gtc gtc gag 402	
50	Asp Glu Ala Pro Leu Leu Ala Thr Tyr Ser Leu Lys Pro Val Val Glu	
•	10	
	but it all all all all all all all all all al	
	The Arm Arm Ala Car Tia Cla Val Clu The Arm Ach Ila Car	
55	Ala Phe Ala Ala Thr Ala Gly Ile Glu Val Glu Thr Arg Asp Ile Ser 30 35 40	

: 43

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Englished States of Cardy

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										ttc								498
		Leu	Ala	Gly	_		Leu	Ala	Gln	Phe	Ala	Asp	Gln	Leu		Glu	Glu	•
5					45					50					55			5 A/O
										gag								546
		Gin	Lys	Va 1		Asp	Ala	Leu	65	Glu	Leu	GIY	GIU	теп 70	Ala	Lys	inr	•
		·ccc				atc	atc	220		c c c	aac	atic	tec		tee	σta	cca	594
10			-	_						Pro								934
			75			110		80					85			1 .	110	
		cag			gci	gcc	gla			clg	cag	gaa		ggc	tac	gac	ctg -	642
15				-													Leu ·	
		90		,			95					100					105	
	•	ссс	gag	tac	gag	gat	gcc	aag	gac	cgc	tac	gcc	gc t	gtc	atc	ggc	tcc	690
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		Asn	Val	Asn		Val	Leu	Arg	Glu	Gly	Asn	Ser	Asp	Arg		Ala	<b>bio</b>	
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		Va, I	Ala			Asn	Phe	Val		Lys	Phe	Pro	HIS		Met	Gly	Glu	
	v	4	4	140					145	-11				150	~~~	~~~		021
20										gt t Val								834
30		пр	155	nia	v2h	261	ГÀŻ	160	4211	741	піа	1111	165	Uly	MId	W2h	изр	
		ttc		agc	aat	gag	aag		gig	atc	atg	gac		gcc	gac	acc	gtg	882
										lle								
35		170	0				175					180					185	,
		gig	a.t c	aag	cal	gtc	gcc	gcc	gac	ggc	acc	gag	acc	glg	ctc	aag	gac	930
		Va l	He	Lys	His	Val	Ala	Ala	Asp	Gly	Thr	Glu	Thr	Val	Leu	Lys	Asp	·*.
					٠.	190			• •		195			. 7	. :	200		
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				220		4:			225					230				1024
										cac								1074
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		-4-	235					240		. 1.	- 4 -	-1-	245					
										Cac								1122
•		250	361	w2h						п15				Ald;			Ala 265	
55			a i c	120						cag								1170
		gal	gil	idl	gia	cag	iac	55 l	gag	cag	ULB	CIL	guu	BUU	550	CIC	uac	1110

	, A n =	Val	Tur	Ala	Cln	Tur	Clv	Glu	Gln	Len	Len	Ala	Ala	Glv	Leu	Asn	
	ASP	441	1 9 1	nia	270	1 7 1	013	0.0		275					280		
		<b>202</b>				acc	orr.	atc			ggc	ctg	gac	aag		gac .	1218
5	gg i	Sq2	Acr	C1"	Fan	Δla	Ala	lle	Tvr	Ala	Glv	Leu	Asp	Lvs	Leu	Asp	*
	GIY	GIU		285	Leu	діа	W. C.	110	290		.,			295			
					atc	220	ara	gcc		Par	аар	ggc.				ggc	1266
	Aar	ggı	gcc	Clu	Ilo	Tve	Ala	Ala	Phe	Ásn	Lvs	Glv	Leu	Glu	Glu	Glv	
10	ASII	GIY	300	Giu	11.6	د پر پر	MIG	305	1110		-, -		310				
		, 700		ac c	a for	σίσ	aac	icc	acc	225	ggr.	atc		aac	ctg	cat	1314
	Dec	Bac	Lau	Ala	Met	Val	Ásn	Set	Ala	Lvs	Glv	lle	Thr	Asn	Leu	His	
•	FIU	315	Leu	Ala	III C I	141	320	,5C1	,,,,			325					
15	a t a	910	t c c	ga t	atr	atr		oac	orr.	toc	atg		gcc	atg	atc	cgc	1362
o i se e e o o	Val	D+0	CAT	Acn	Val	ما ا	He	Asp	Ala	Ser	Met	Pro	Ala	Met	Ile	Arg ·	
	330	110	261	лэр	, 41	335	110	1100			340					345	
•		100	aać	220	210		áac	aag	gac	gac		асс	cag	gat	gc c	ctg	1410
20	The	Sar	Clv	lvc	Mel	Trn	Asn	Lys	Asp	Asp	Gln	Thr	Gln	Asp	Ala	Leu	
		.961	. 013	LJJ	350			_,		355		٠.		: .	360		
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	He	Trp	Arg	Ala	Cys	·Gln	Thr	Lys	Asp	Ala	Pro	He	Gln	Asp	Trp	Val	
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.*.	aag	ctg	gct	gtc	aac	cgc	gca	cgt	ctc	tcc	ggc	atg	ccc	gc t	gtg	ttc	1746
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	Trp	Leu	Asp	Pro	Ala	Arg	Ala	His	Asp	Arg	Asn	Leu	Thr	Thr	Leu	Val	
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<i>55</i>	Glu	Lys	Туг	Leu	Ala	Asp	His	Asp	Thr	GJu	Gly	Leu	Asp	He	Gln	lle	

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	490	)		٠.		495	· ·.			•	500					505	
			ccc	gic	gag	gcc	acc	cag	cac	gcc	atc	gac	cgc	atc	cgc	cgc	1890
5					Glu												
5			*:	-	510		٠			515		**	•		520		٠ ;
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	Thr	Asp	Leu	Phe	Pro	He	Leu	Glu	Leu	Gly	Thr	Ser	Ala	Lys	Me t	Leu	·
		:	540		,		:	545					550				
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	Leu	Arg	Trp	ASP	Ser	Leu	Gly	Glu	Phe		Ala	Leu	Ala	GIU			
25					590					595		,			600	· ;	9170
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	Arg	піз		.605	ASII	1111	ALG.	W2 II	610	1111	Lys	nia	GI-y	615		Ald	
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				:	Arg												2220
	1150		620		****		• ;•••	625		,			630		<b>D J G</b>	111	
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					Trp												
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	Glu	Leu	Ala	Glu	Thir	Phe	Ala	Pro	Val	Ala	Glu	Ala	Leu	Asn:	Asn	Gln	
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     Thr Tyr Ser Leu Lys Pro Val Val Glu Ala Phe Ala Ala Thr Ala Gly
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                                           30
     lle Glu Val Glu Thr Arg Asp Ile Ser Leu Ala Gly Arg Ile Leu Ala
                     40
     Gln Phe Ala Asp Gln Leu Pro Glu Glu Gln Lys Val Ser Asp Ala Leu
            55
     Ala Glu Leu Gly Glu Leu Ala Lys Thr Pro Glu Ala Asn Ile Ile Lys
            70
                                    75
     Leu Pro Asn Ile Ser Ala Ser Val Pro Gln Leu Lys Ala Ala Val Lys
              85
     Glu Leu Gln Glu Gln Gly Tyr Asp Leu Pro Glu Tyr Glu Asp Ala Lys.
               100
                                   110
     Asp Arg Tyr Ala Ala Val Ile Gly Ser Asn Val Asn Pro Val Leu Arg
40
               120
     Glu Gly Asn Ser Asp Arg Arg Ala Pro Val Ala Val Lys Asn Phe Val
            135
                              140
     Lys Lys Phe Pro His Arg Met Gly Glu Trp Ser Ala Asp Ser Lys Thr
                     150
     145
     Asn Val Ala Thr Met Gly Ala Asp Asp Phe Arg Ser Asn Glu Lys Ser
                  165
     Val Ile Met Asp Glu Ala Asp Thr Val Val Ile Lys His Val Ala Ala
                              185
                     180
     Asp Gly Thr Glu Thr Val Leu Lys Asp Ser Leu Pro Leu Leu Lys Gly
     200 200 205
     Glu Val lle Asp Gly Thr Phe lle Ser Ala Lys Ala Leu Asp Ala Phe
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	210		215			220	
Le							Leu Phe Ser
22		•					240
5 Al	a His Me						lle Ile Phe
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GI	y His II	e Val Arg	Ala Tyr	Phe Ala	Asp Val	Tyr Ala	Gin Tyr Gly
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Gli							Leu Ala Ala
•		5				285	
110		a Gly Leu					lle Lys Ala
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		p Lys Gly					Met Val Asn
305		o Cly Ilo		Lau Hic			320 Val Ile Ile
	HIA LY	325		rea mis		Sei Hah	•
20 A S r	o Ala Se						Met Trp Asn
7.5				345			350
Lys	Asp As						Asp Ser Ser
25		5					• • • • •
Ty							Lys Asn Gly
		· · · .					
							Gly Leu Met
30 385				Q1			400
Ala	i Gin Ly	S Ala Glu	Glu lyr	Gly Ser	HIS ASD	Lysinr	Phe Arg Ile
Cla	ι Ala Δc						415 Asp Val Leu
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Lys							Asn Arg Ala
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Glu							Leu Met Ala.
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             580
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                                                   605
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                  660
       Pro Val Ala Glu Ala Leu Asn Asn Gln Ala Ala Asp Ile Asp Ala Ala
           675 680
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	Val	Leu	He	Ser		Gly	Phe	Arg	Pro	-	Val	Glu	Gly	Phe	,		• • • • •	
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	430 435 440	
•	age ege age gie cae ate cae eeg ace etg teg gag get gie aag gaa	176
	Ser Arg Ser Val His Ile His Pro Thr Leu Ser Glu Ala Val Lys Glu	
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' <i>50</i>	lle Val Gly Gly Gly Ala Ile Gly Met Glu Phe Ala Tyr Val Leu Gly	
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55	Pro Asn Glu Asp Pro Glu Val Ser Lys Val Ile Ala Lys Ala Tyr Lys	

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		Lys																1100	
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		Glu																. 200	
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	Val	Рго-	Asp.	His															•
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				Leu														
				450	8	٠.٠								460				
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	His Pro Ile Pro Phe Asn Arg Leu Arg Asp Ala Phe Asp Gly Tyr Pro
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50	Met Phe Gin Gin Phe Lys Lys Asp Pro Gin Ser Val Asp Lys Glu Trp 20 25 30  Arg Glu Leu Phe Glu Ser Gin Gly Gly Pro Gin Ala Glu Lys Ala Thr 35 40 45  Pro Ala Thr Pro Glu Ala Lys Lys Ala Ala Ser Ser Gin Ser Ser Thr 50 55 60  Ser Gly Gin Ser Thr Ala Lys Ala Ala Pro Ala Ala Lys Thr Ala Pro 65 70 75 80
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10	Glu Glu Ile Leu Phe Val Gln Asp Glu Pro Ala Asn Gln Gly Ala Trp
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15	Met Arg Arg Ile Ser Arg Arg Ser Gln Ser Ser Thr Ala Thr Gly Ile 1205 1210 1215
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50	
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	72207 Description of Artificial Sequence, prime, for access	
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	(223) Description of Artificial Sequence: primer for dtsRl	
	<b>&lt;400&gt;</b> 39	
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	acgettage origination	
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40	<211> 20 (212) 204	
	(212) DNA	
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50	*D**G**** * * * * * * * * * * * * * * *	
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55	<212> DNA	
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25	<b>&lt;210&gt; 43</b>
25	<b>&lt;211&gt; 20</b>
	(212) DNA
, X	<213> Artificial Sequence
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	(223) Description of Artificial Sequence, primer for pix
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			cag Gln														288	
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20			Ser														. 436	
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. 25	Arg	Phe	Cys	Gln	Ser	Phe	Met	Thr	Glu	Leu	His	Arg	His	Ile	Gly	Glu	••	
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	gaa tc	t tig.	aag	. a t.c	gtc	ctg	gaa	aag	gac	.cct	cat	tac	gct	gat	y tac	144	111
35	Glu Se	r Leui	Lvs	He.	Val	Leu	Glu	Lvs	Asp	Pro	His	Туг	Ala	Asp	Туг		,
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•	Gly Le	ı Ile	Gln	Arg	Leu	Суs	Glu	Pro	Glu	Arg	Gln	Leu	He	Phe	Arg		
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45	cgc gt	r cap	110	aac	101	gca	ctt	gga	cca	tac	aag	ggc	ggc	cig	cgc	288	
	Arg Va																
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•	Gln II	e Phe	Lvs	Asn	Ser	Leu	Thr	Gĺv	Leu	Pro	lle	Gly	Gly	Glv	Lys		
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5	•	130	)				135			٠	• • •	140										
-	cg	1.110	tgc	cag	lcc	1 t-c	alg	acc	gag	cig	cac	cgc	cac	a!c	ggi	gag		480				
		g Phe	e Cys	Gln	Ser	Phe	Met	Thr	Glu	Leu	His	Arg	His	lle	Gly	Glu	•				•	
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10	t a	ccgc	gac	gii	cct	gca	ggt	gac	atc	gga	gti	ggt	ggc	cgc	gag	atc		528				
	Ty	r Arg	Asp			Ala	Gly	Asp	He	Gly	Val	Gly	Gly	Arg	Glu	Ile						
					165				٠	170					175					•		
	gg	l lac	ctg	111	ggc	cac	tac	cgt	cgc	alg	gct	aac	cag	cac	gag	tcc		576				
15	• G1	y Tyr	Leu		Gly	His	Туг	Arg		Met	Ala	Asn	Gln		Glu	Ser					• •	
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30	Ser	Gly	Asn	Val	Ala	The	Tvr	Ala	lle	Clu	luc	Ala	Cln	Clu	Lon	ggc	. (	768				.PDE /ER
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		Arg															****		· · · · · · · · · · · · · · · · · ·			
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50	Ala	Thr	Gln	Asn	Glu	Leu	Asn	Gly	Glu	Asn	Ala	Lys	Thr	Leu .	Ala	Αέρ	•		•			
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	Asn	Gly	Cys	Arg ]	Phe !	Val	Ala	Glu	Gly	Ala	Asn	Met	Pro :	Ser	Thr.	Pro	i					
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	gag	gc t	gtt	gag	glc	ttc	cgt	gag	cgc	gac	atc	cgc	ttc .	gga	cca	ggc	1	104	•			

	Glu	Ala	Val	Glu	Val	Phe	Arg	Glu	Arg	Asp.	He	Arg	Phe	Gly	Pro	Gly		
			355		•			360	. , 1		•.	• • •	365			;		
	aág	gca	gct	aac	gct	ggt	ggc	gtt	gca	acc	tcc	gcl	ctg	gag	alg	cag	1	152
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		370					375					380		٠., .		<i>.</i>		
· .	cag	aac	gct	tcg	cgc	gat	t-cc	tgg	agc	llc	gag.	lac	acc	gac	gag	cgc	1	200
10	Gln	Asn	Ala	Ser	Arg	Asp	Ser	Trp	Ser	Phe	Glu	Tyr	Thr	Asp	Glu	Arg		
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	ctc	cag	gtg	atc	atg	aag	aac	atc	1-1 C	aag	acc	tgt	gca	gag	acc	gca	1	248
	Leu	Gln	Val	He	Met	Lys	Asn	He	Phe	Lys	Thr	Cys	Ala	Glu	Thr	Ala		•
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	Ala	Glu	Tyr	Gly	His	Glu	Asn	Asp		Val	Val	Gly	Ala	Asn	He	Ala		
•				420	:				4.25	(				430				
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•	Gly	Phe	Lys	Lys	Val	Ala	Asp		Met.	Leu	Ala	Gln		Val	He			
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30	<40	0> 8:	2					•		Т	. ; T	100	No.	Ton	Lon	Luc	****	
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	145					150					155				٠.	160	•			
		Arg	Arn	Val													·			
		Λιg		va i	165		Oly	nsp	110	170				VI B		110				
5	Cly	Туг	Lau	Dha			Tur	Δεσ	Δřσ							Sar				
	Gry	1 9 1	Leu	180					185		nia		. 0111	190	Giu	361				
	Cly	V - I	·Lan										202		Val	Arg.				
	GIY	141			GIY		Uly	200	1111	H	UI,	Uly	205	LCU	1 4 1	WIE.	• :	,		
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	Luc	210 Ala	1 2/0	Clar	Cla	°			ČLv	Cla	Lvc		Ilo	Val	Sar.	Clu.				
	225	Ald	L y S	GIY.	GIU	230		361	GIY			116				240				
15		Gly	Acn	Val	Ala			A 1 2	I l o	G1 ii										•
	261	Gly	M311	1 4 1	245	1111	1 9 1	ліа	116		Lys					Oly				
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	Ala	1 11 1	V a 1	260		rne	251	изр	265		GIY.									
20		Gly	Val			Ala	Luc	Lon									,	*		
	ASII		275	W2h	Yal	Ald	L y S	280	MIG	GIU	116			Val	Arg	Alg	•			
	Alo			S 0 F	Val	Tur	A1 a		Cla	110	Clu	Cly	285	Th.	T.,,	шіс		. ,		
		Arg 290			141				GIU			300	піа	1 11 1	1 9 1	п12	•			-, *
25	Th.	Asp											Ala	Lan	Dro	Care				
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		Thr	Cln	Acn	Gla									ien	ΔΙа			•		-
30	Ald	1 11 1	GIII	W211	325		<b>L211</b>	Gly	oru	330	піа	Lys	1111	ren	335	nsp		•		
30	as A	Gly	Cve	A = ~			Ala	Clu	Clu		Acn	Mat	Dro	202		Dro	,			,
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5		Val	Ala	Ser	Asp	Asn	Asn	Lys	Ala	Val	Leu	His	Туг	Pro	Gly	Gly	Glu		,
		1			٠.	5					10	٠,				. 15	·		
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		Phe	Glu	Met	Gly	He	Lys	Gln	Ala	Thr	Glu	Gly	Asn:	Ser	Gly	Val	lle		
10			٠,		20					25				· ;	30		٠.		٠.
		ctg	ggt	aag	atg	ctg	tcg	gaa	acc	ggt	cig	gtc	acc	ttc	gac	ccc	ggt	144	
		Leu	Gly	Lys	Met	Leu	Ser	Glu	Thr	Gly	Leu	.Val	Thr	Phe	Asp	Pro	Gly	•	
			•	35		. *			40					45		,			• ;
15	*	tat	gtc	agc	acc	ggt	tcc	acc	gaa	tcc	aag	atc	acc	tac	atc	gat	ggt	192	
4.0		Туг	Val	Ser	Thr	Gly	Ser	Thr	Glu	Ser	Lys	He	Thr	Tyr	Ile	Asp	Gly		, .
			50					. 55	•	•			60						•
20	٠,	gal	gca	ggc	atc	ctg	cgc	tac	cgc	ggc	tac	gac	att	gcg	gat	clg	gcc	240	
20		Asp	Ala	Gly	lle	Leu	Arg	Tyr	Arg	Gly	Tyr	Asp	He	Ala	Asp	Leu	Ala		
		65					70			•		75			· ;		80		•
		gaa	aat	gc.c.	acc	ltc	aat	gag	gtc	tcc	tac	$\cdot ctc$	ctg	atc	aag	ggt	gag	288	
25		Glu	Asn	Ala	Thr	Phe	Asn	Glu	Val	Ser	Ţуr	Leu	Leu	Ile	Lys	Gly	Glu		
						85					90					95	•	. : **	
		c.1 c	ccg	acc	ccg	gaa	gag	ctc	cac	aag	ttc	aac	gac	gag	alt	cgt.	cac	336	
		Leu	Pro	Thr	Pro	Glu	Glu	Leu	His	Lys	Phe	Asn	Asp	Glu	Ile	Arg	His		
30			1.7		100					105					1.10		**	\$4.27.1	-
		cac	acc	ctg	ctg	gac	gag	gac	ttc	aag	tcc	cag	110	aat	gtc	ttc	cct	384	
		His	Thr	Leu	Leu	Asp	Glu	Asp	Phe	Lys	Ser	. Gln	Phe	Asn	Val	Phe	Pro		
			1 .	:115			٠,		120		•		. •	125					•
35		cgc	gat	gc.c.	cac	ccg	,atg	gcc	acc	ctg	gcc	tcc	tcg	gt t	aac	atc	ctc.	432	
		Arg	Asp	Ala	His	Pro	Me.t			Leu	Ala	Ser	Ser	Val	Asn	lle	Leu	• •	
		•	130	* *	•		,	135		,		<b>'</b> ,	140				. '		•
		tcc	acc	tac	tac	cag	gat	cag	ctg	gat	CCC	cig	gat	gag	gcl	cag	ctg	480	
40		Ser	Thr	Туг	Туг	Gln		Gln	Leu	Asp	Pro			Glu	Ala	Gln	Leu		
		145		Ì .		. 3	150		ta j			155		•	**		160	500	•
		gac	aag	gca	acc	gtc	cgc	ctg	alg	gcg	aag	git	. ccg	atg	clg	gct	gca	528	. •
		Asp	Lys	Ala	Thr	Val	Arg	Leu	Met	Ala	Lys	Val	Pro	Met	Leu	Ala	Ala		
45						165		: -		,	170					175			
		lac	gca	cac	cgt	gcc	cgc	aag	ggt	gcg	ccg	tac	aig	tac	ccg	gac	aac	- 576.	
	•	Туг	Ala	His	Arg	Ala	Arg	Lys	Gly			Туг	Met	Туг			Asn.		
					180			• •	•	185		:			190				
50		tcc	cic	aat	gcc	cgt	gag	aàc	tto	Cle	g cgc	alg	alg	tto	ggt	tac	ccg	624	
		Ser	Leu	Asn	Ala	Arg	Glu	Asn			Arg	.Me t	Met	Phe	Gly	Туг	Pro		
٠.				195					200	)				205	,				
		acc	gag	-c.c.g	t-a-c	gag	gt t	gal	C-C {	g- a-1-(	a-1 g	gg.t.c	aaa	gcc	:C.I.C	gac	aag	672	. •
55		Thr	Glu	Pro	Туг	Glu	Val	Asp	Pro	o Ile	Met	Val	Lys	Ala	Let	Asp	Lys	• • ,	•

12.

	0.0			
	210	215	220	*
	ctg ctc atc ctg	cac gca gac cac gag cag	220 too too 000 too 001	7.00
	In In Ite	the gen gue the gug tag	ade the tee ace tee act	720
5	ren ren 116 Fen	His Ala Asp His Glu Gln	Asn Cys Ser Thr Ser Thr	
-	225	230	235 240	
	ate eac sta sta		210	
	gre ege alg att	ggc tcc gcg cag gcg aac	aig lic gic tcc aic gcc	768
	Val Arg Met Ile	Gly Ser Ala Gln Ala Asn	Met Phe Val Ser Ile Ala	
		245 ( 250		
10		· · · · · · · · · · · · · · · · · · ·	255	·
	gge gge ale aac	gca cic icc ggc ccg cig	cac ggt ggc gcc aac cag	816
	Gly Gly Ile Asn	Ala Leu Ser Gly Pro Leu	His Gly Cly Ala Acn Cln	Company of the Company
	260		and the second s	
		265	270	
15	get gie ete gag	atg ctc gag gag atc gca	gcc aac ggc ggc gac gca	864
	Ala Val Leu Glu	Met Leu Glu Glu Ile Ala	Ala Asn Cly Cly Asn Ala	
	275			
	A Company of the Comp	280	285	
	acc gac itc aig	aac cgc gig aag aac aag	gag aag ggt gtc cgr ctr	912
20	The Asp Phe Met	Asn Arg Val Lys Asn Lys		312
	noo The life t			
	290	295	300	
٠.	atg ggc ttc gga	cac cgc gic tac aag aac	tac gat erg egt gea gee	960
*.	Met Gly Phe Gly	Hic Arg Val Tur Lug Ann	From Ann Des Ann All All	300
	not dry the dry	His Arg Val Tyr Lys Asn 1		
25	305	310	315 320	
	atc gtc aag gac	acc gcc cac gag alc ctc g	EAR CAC CIC PPI POC PAC	1008
	The Val Lys Asp	The Ala His Clu Ho Lou	No His Ison Cl. Cl.	1000
* .	iic var Eys.nsp	Thr Ala His Glu lle Leu (	ilu nis Leu Gly Gly Asp.	
		325 330	335	
30	cca cig cig gat	cig got oto aag oig gaa g	raa ate gea ete aar gar	1056
	Pro Leu Leu Aso I	Leu Ala Leu Lys Leu Glu G	'In Ile Ale Leu Assidant	
	2.0 202 202 1139 1		id lie Ala Leu Ash Asp	
	340	<b>7.</b> 0	350	
	gat tac tic atc	tee ege aag etg tae eeg a	ac glg gar tir tar arr	1104
35	Asp Tyr Phe Ile 9	Ser Arg Lys Leu Tyr Pro A	on Vol Are Dhar Toll Ti	
	חבר:			
	355	360	365	
	ggc cig aic tac o	ege gee atg gge ite eeg a	og gad lie lie are gie	1152
	Gly Ien He Tur A	Ara Ala Mat Cly Pho Pro T	he Ass Dhe Dhe Ti II I	1106
40	ory Eco Tie Tyl P	Arg Ala Met Gly Phe Pro T		
	370	375	380	
	clg_ltc_gcc_atc_g	ggc_cgc_ctc_ccg_ggc_tgg=a	1c-gcc-cac-tac-cac-aaa-	_1-2.0.0
	len Phe Ala Ida C	ly Arg Ion Dro Clar Tro I	la Alla III m	1200
	non	Gly Arg Leu Pro Gly Trp I	ie Ala nis lyr Arg Glu	
45	385	390	95 400	
45	cag ctc gcc gal c	cg ggc gcc aag atc aac c		1940
	Cin Lon Ala Aca B	les Claratte Las III A	green ege cag are rac	1248
	GIII Leu Ala ASP P	ro Gly Ala Lys Ile Asn A	rg Pro Arg Gln Ile Tyr	
1	4		415	
	acc ggl gag acc g	ca ege aag ate ate eee e	GC G23 G2G 0G0 10G	1000
50	The Cly Clu The A	le App Top 11: 11: 5	er eag kak rkr isk	1293
		la Arg Lys lle lle Pro A	rg Glu Glu Arg 🚎 🐇 🐪 🛒	
	420	425	430	
			100	
	(210):00			
55	<210> 90			
	<211> 430			

# <212> PRT

# <213> Corynebacterium thermoaminogenes

5	·	<400	0> 90	) .			χ. '			•			•			•	
	+ * ·	Val	Ala	Ser	Asp	Asn	Asn	Lys	Ala	Val	Leu	His	Tyr	Pro	Gly	Gly	Glu
•••		1				5		, , , ,			10			**		1.5	
		Phe	Glu	Met	Glv	He	Lys	Gln	Ala	Thr	Glu	Gly	Asn	Ser	Gly	Val	Ile
10					20					25					30	* * •	
		Len	Glv	Lvs			Ser	Glu	Thr	Gly	Leu	Val	Thr	Phe	Asp	Pro	Gly
•	: :	200		35					40					45			:
٠.		Tvr	.Val			Glv	Ser	Thr	Glu	Ser	Lys	He	Thr	Tyr	He	Asp	Gly
15			50		- • • •				,		•	. 4:	60			. , .	•
		Asp		Glv	ile	Leu	Arg	Туг	Arg	Gly	Туг	Asp	lle	Ala	Asp	Leu	Ala
		65		J.,			70					75			٠		80
		Glu	Asn	Ala	Thr	Phe	Asn	Glu	Val	Ser	Tyr	Leu	Leu	He	Lys	Gly	Glu
20		0.0				. 85					90		, ,			9.5	
		Leu	Pro	Thr	Pro		Glu	Leu	His	Lys	Phe	Asn	Asp	Glu	He	Arg	His
					100		• •			105					110		·. : '
25		His	Thr	Leu	Leu	Asp	Glu	Asp	Phe	Lys	Ser	Gln	Phe	Asn	Val	Phe	Pro
	•			115					120		•			125			
		Arg	Asp	Ala	His	Pro	Met	A.la	Thr	Leu	Ala	Ser	Ser	Val	Asn	l l e	Leu
			130				•.	135					140				
. 30		Ser	Thr.	Tyr.	Tyr	Gln	Asp	Gln	Leu	Asp.	$. {\tt Pro}$	Leu	Asp	Glu	Ala	Gln	Leu
		145					150					155			•		160
		Asp	Lys	Ala	Thr	$\cdot v_{a\cdot l}$	Arg	Leu	Met	Ala	Lys	Val	Pro	Met-	Leu	Ala	Ala
			٠.			165		*5			170					175	
35		Туг	Ala	His	Arg	·Ala	Arg	Lys:	Gly	Ala	, Pro	Tyr	Met	Tyr	Pro	Asp.	Asn
					180		•			185					190		
		Ser	Leu	Asn	Ala	Arg	Glu	Asn	Phe	Leu	Arg	Met	Met			Туг	Pro-
			,	195			•		200				1.00	205	`* · ·		
; 40 ;		Thr	Glu	Pro	Туг	Glu	Val	Asp	Pro	He	Met	Val	Lys	Ala	Leu	Asp	Lys
		:.	210	· ·	,			215					220				
	•	Leu	Leu	He	Leu	His	Ala	Asp	His	Glu	Gin	Asn	Cys	Ser	Thr	Ser	Thr
		225		•			230					235					240
45		Val	Arg	Met	He	Gly	Ser	Ala	Gln	Ala	Asn	Met	Phe	Val	Ser	lle	Ala
							i:										
		Gly	Gly	He	Asn	Ala	Leu	Ser	Gly						Alà	Asn	Gln
_:					260										270		
50		Ala	Val	Leu	Glu	Me t	Leu	Glu			Ala	Ala	: Asn	Gly	Gly	Asp	Ala
				275		•	•	-	280			··		285			
		Thr	Asp	Phe	Met	Asn	ı Arg	Val	Lys	Asn	Lys	Glu	Lys	Gly	Val	Arg	Leu
			- 290	1-1				- 295	·			الماييات	_ 3.0.0	) <u>-</u>	.i		
55		Met	Gly	Phe	Gly	His	Arg	, Val	Tyr	Lys	Asn	Tyr	Asp	Pro	) Arg	, Ala	Ala

# EP 1 219 712 A1...

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	305	310	315	20
	lle Val Lys Asp Thi		Glu His Leu Gly Gly A	SD.
_	325	330	335	•
5	Pro Leu Leu Asp Leu	Ala Leu Lys Leu Glu	Glu Ile Ala Leu Asn A	SD
	340	345	350	
	Asp Tyr Phe Ile Ser		Asn Val Asp Phe Tyr T	hr
10	355	360	365	
	370		Thr Asp Phe Phe Thr V	al
		375	380	
_	385	390	lle Ala His Tyr Arg G 395	
15			40 Arg Pro Arg Gln Ile Ty	)U
	405	410	415	<b>/I</b>
	Thr Gly Glu Thr Ala	Arg Lys Ile Ile Pro A	Arg Glu Glu Arg	
20	420	425	430	
	(210) 91			
	(211) 1314			
25	<212> DNA			
	(213) Brevibacterium	lactolermentum		
	⟨220⟩			
<i>30</i>	⟨221⟩ CDS			
	(222) (1)(1311)			25- 49
	<400> 91			
35	atg itt gaa agg gat	atc gtg gct act gat a	ac aac aag got gio ci	g 48 5
	met Phe Glu Arg Asp	lle Val Ala Thr Asp A	sn Asn Lys Ala Val Le	1
		10		
40	His Tur Pro Clu Clu	gag ile gaa aig gae a	to ato gag got tot ga	g 96
	20	oru Prie Gru Met ASP 1. 25	le Ile Glu Ala Ser Gli	
			30	
	Gly Asn Asn Gly Val	al len Gly Lys Met La	tg tot gag act gga ctg eu Ser Glu Thr Gly Lev	g 144
45	35	40	45	
			gc tcc acc gag tcg aag	192
	Ile Thr Phe Asp, Pro (	ly Tyr Val Ser Thr GI	y Ser Thr Glu Ser Lys	136
	50	55	60	
50	atc acc tac atc gat g	gc gat gcg gga atc ct	g cgt tac cgc ggc tat	240
	lle inr lyr lle Asp (	ly Asp Ala Gly lle Le	u Arg Tyr Arg Gly Tyr	,
•	65	70	5	
55	gac atc gct gat cig g	ct gag aal gcc acc it	c aac gag gil ici lac	288
	Asp Ile Ala Asp Leu A	la Glu Asn Ala Thr Ph	e Asn Glu Val Ser Tyr	
				•

			: .					٠,	1.4						0.5			
•	. *				85			*		90					95		0.00	
	cta	ctt	atc	aac	ggt	gaa	cla	cca	acc	сса	gat-	gag	ctt.	cac	aag	ttt	336	
- t- t	Len	Leu	He	Asn	Glv	Glu	Leu	Pro	Thr.	Pro	Asp	Glu	Leu	His	Lys	Phe	· .	
5	LCU	LCu		100	• • •			٠.٠.	1.05			, ,		110	· .			
		gac		100	200	cac	cac			clø	gar	gag	gac	ttc	aag	tcc	384	٠,
•	aac	gac	gag	all	cgc	tat	uic	The	Lan	Lan	Acn	Clu.	Acn	Phe	Lve	Set		
	Asn	Asp		He	Arg	HIS			Leu	LEU	MSD.	GIU	105	1 116	Lys.	501		
		* * **	115		• •			120		•			125				400	:
10	cag	ttc	aac	gtg	ttc	cca	cgc	gac	gc t	cac	cca	atg	gca	acc	ııg	gcı	432	
	Gln	Phe	Asn	Val	Phe	Pro	Arg	Asp	Ala	His	Pro	Met	Ala'	Thr	Leu	Ala		
		130		÷					٠		. :	140		· · .	, , , <del>, , '</del>			٠.
	too	tcg	σt t	áac	ätt	. ttg	tet	acc	tac	tac	cag	gat	cag	ctg	aac	cca	480	
15	200	Ser	Val	Ace	Ila	Lau	Car	Thr	Tyr	Tur	Gin	Asp	Gln	Leu	Asn	Pro		
		261	Val	ASII	116		301	1111			155				. ,	160	y	
	145				, ;	150						0.00	ctc	a for			528	
	ctc	gat	gag	gca	cag	CII	gaı	aag	gca	acc	gii	tgt 4		Mat	Ala	Tuc	. 020	•
20	Leu	Asp	Glu	Ala	Gln	Leu	Asp	Lys	Ala	ınr	vai	Arg	reu	mei	Ald	Lys.		
			•.		165	:				170				•	175			• • •
	gtt	cca	atg	ctg	gct	gcg	tac	gca	cac	cgc	gca	.cgc	aag	ggt	gc t	cct	576	• • •
	Val	Pro	Met	Leu	Ala	Ala	Тут	Ala	His	Arg	Ala	Arg	Lys	Gly	Ala	Pro		' . <i>'</i>
				180		3.			185					190	·			
<i>25</i>		atg	tan		a a c	220	tee				cgi	gag	aac	ttc	cig	cgc	624	1
	, i a c	Met	T	Dag	A'an	Acn	Cor	Lau	Acn	Ala	Arg	Glu	Asn:	Phe	Leu	Arg	,	
	lyr	Met		PTO	ASD	. <b>M</b> 211	 3E1	200	АЗП	7114	1116	0.0	205					
			195		7.									663	atr	a to	672	
30	atg	atg	ttc	ggt	tac	cca	acc	gag	cca	lac	gag	alt	gat	D-a	Ila	atg	0.2	
• •	Met	Met	Phe	Gly	Туг	Рго			Pro	Туг	611	116	ASD	PIO	116	met		
		210					215					220			•		- ·	
•	gtc	aag	gcl	ctg	gac	aag	cig	ctc	atc	ctg	cac	.gct	gac	cac	gag	cag	720	i •
35	Val	Lvs	Ala	Leu	Asp	Lys	Leu	Leu	lle	Leu	His	Ala	Asp	His	Glu	Gln '	· .	
55	225					230					235					240		
	220	tac	100	300	trr			cgt	atg	atc	ggı	tcc	gca	, cag	gcc	aac	768	}
	aat	. rec	205	The	Car	The	Val	Аго	Met	He	- G1 v	Ser	Ala	Gln	Ala	Asn		•
• • • • •	ASII	Cys	261	1 11 1			, , ,	111.6		250		-	. •		255		* 1	
40	1.				245	'						cto	100	a <b>a</b> c			816	3
	alg	ttt	gtc	tcc	ald	gct	gg	ggo	alc	aau	gu	1		66	. D-0	cig	0.0	
- 1	Met	Phe	Val	Ser	116	Ala	Gly	Gly	He	Asn	Ala	Leu	Ser	61)	. PIU	Leu		
	•			260	)									270				
45	cac	ggt	ggc	gca	aac	cag	gct	g11	ctg	gag	g at g	cto	gaa	gao	ato	aag	864	ł
	His	Glv	Glv	Ala	Ast	Glr	Ala	ı Val	Leu	Glu	Met	Leu	Glu	Ast	116	Lys	•	
1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	1113		275		:			280	)				285		•		.*	
				) (1							ats	z áac	: ลลย	gt	c⊸aas	aac	912	2.
50	aac	aac	cac	ggı	r - BB	, gai	, gu	1. act	. 60E	Dha	Mo	Λοι	lve	Va	live	AST		
30	Asr			613	/ 613	ASI	Ala	1 (B) -	Alc	rne ;	, MC	000	, rito	, u		Asn		
•		290	)				295		••			00.		**			ne	n
•	aag	g gaa	gad	gg	c gi	c cg	cte	c at	gʻgg	: 110	gg	a ca	cgo	g t	ı la	aag	960	
	Lys	s -G-I-u	ı-Asr	- G1:	y Va	1A r.1	g Lei	u.Me.	L_G1	/_Phe	e_G_l :	<u>y Hi</u> :	s Arg	y <u>v</u> a	1 . l <u>y</u>	L LYS		:
55	308		,			310					31	5				320		
	500	-	•		- 1			,								-		

		aa	ic t	ac i	gai	cca	ı. cgi	gca	gca	ato	gt	c aas	gas	z acc	gra	cac	· σ20	atc	100	0		
		Ac	n T	vr /	A en	Pro	Arc	• Ala	. Δla	ه ا ا	Val	Luc	Cli	, Th-	. 41.	17:-	, Pre	ille	100	0		
		710	11 1	3 1 1	13 p				, Ala	. 110	va.			1 1111	Ala	πιs						
5							325					330						*				
3		c t	c g	ag (	cac	ctc	ggt	ggc	gac	gal	cti	t ctg	gal	clg	gca	atc	aag	ctg	105	6		
		Le	u G	lu F	lis	Leu	Gly	Gly	Asp	Asp	Leu	ı Leu	Asp	Leu	Ala	He	Lvs	Leu				
						340							•	1		350						
		σa	а <i>с</i> т:	22 2														, ,				
10		CI	u 6	1 t		gla	rig	gu	gal	gaı	lac		att	100	cgc	aag	CIC	tac	110	4		
		- 61	u G.			Ala	Leu	Ala	Asp			Phe	He	Ser	Arg	Lys	Leu	Туг				Ť
				3	55	-				360	•			:.	365							
		CC.	g aa	ac g	t a	gac	ttc	tac	acc	ggc	c't g	alc	tac	cgc	дса	atg	ggr	ttc	115	)	•	
		Pr	o As	n V	a l	Asp	Phe	Ťνr	Thr	Glv	Len	lle	Tvr	Δισ	Ala	Mat	Cly	Phe	110	,		
15			37	70		p			375				1 7 1			met	GIY	rne	;	* : :		
														380					• •			
		-00	a at	ιg	ac	ιιc	llc	acc	gta	llg	ttc	gca	atc	ggt	cgt	cig	cca	gga	1200	)		
		Pro	) Th	IT A	SP.	Phe	Phe	Thr	Val	Leu	Phe	Ala	He	Gly	Arg	Leu	Pro	Gly				
20		388	5					390	•				.395					.400				
		tgg	g at	c g	c t 🦠	cac	tac								ggr	aac	220	atc	1248			7.1
		Trr	. []	e A	la l	Hic	Tvr	Δισ	Gla	Cln	Tair	Clv	Ala	412	C1	4	Las	Ile:	1240	•		
		•••	•	· //			405	мь	014	0111	reu		nia	Aid	GIY,	AS II		11e				
				•		•				• • •		410		14			415					•
25	•	aac	cg:	C C	ca (	cgc	cag	gtc	tac	acc	ggc	aag	gaa	tcc	cgc	aag	itg	gtt	1296	;		
		Asn	ı Ar	g P	ΓΟ.	Arg	Gln	Val	Туг	Thr.	Gly	Lys	Glu	Ser	Arg	Lys	Leu	Val	٠			e i digi
			•			120																1.50
		cct	Сg	c ż	ag s	282	cgc	taa								,00			1214			
30							Arg							100					1314	•	•	
30		110	711			3 1 U	nig						٠.	•		•	•					
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35		<21	1>.4	437				;	•						,							·
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	9.698.400.66 t

#### Claims

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- 1. A protein having the amino acid sequence of SEQ ID NO: 2 or the amino acid sequence of SEQ ID NO: 2 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, which has isocitrate lyase activity and shows 30% or more of residual activity after a heat treatment at 50°C for 5 minutes.
- 2. A protein having the amino acid sequence of SEQ ID NO: 4 or the amino acid sequence of SEQ ID NO: 4 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, which is involved in acyl Co-A carboxylase activity and is derived from *Corynebacterium thermoaminogenes*.
- 3. A protein having the amino acid sequence of SEQ ID NO: 6 or the amino acid sequence of SEQ ID NO: 6 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, which has DtsR activity and is derived from *Corynebacterium thermoaminogenes*.
- 4. A protein having the amino acid sequence of SEQ ID NO: 8 or the amino acid sequence of SEQ ID NO: 8 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, which has DtsR activity and is derived from Corynebacterium thermoaminogenes.
  - 5. A protein having the amino acid sequence of SEQ ID NO: 10 or the amino acid sequence of SEQ ID NO: 10 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, which shows phosphofructokinase activity at 60°C in an equivalent or higher degree compared with the activity at 30°C.
  - 6. A protein having the amino acid sequence of SEQ ID NO: 94 or the amino acid sequence of SEQ ID NO: 94 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, which has activity for imparting sucrose assimilating ability to *Corynebacterium thermoaminogenes*.
  - 7. A protein having any one of the amino acid sequences of SEQ ID NOS: 17-20 or the amino acid sequence of any one of SEQ ID NOS: 17-20 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, which has a function involved in glutamic acid uptake and is derived from Corynebacterium thermoaminogenes.
  - **8.** A protein having the amino acid sequence of SEQ ID NO: 22 or the amino acid sequence of SEQ ID NO: 22 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, which has pyruvate dehydrogenase activity and is derived from *Corynebacterium thermoaminogenes*.
  - 9. A protein having the amino acid sequence of SEQ ID NO: 24 or the amino acid sequence of SEQ ID NO: 24 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, which has pyruvate carboxylase activity and is derived from *Corynebacterium thermoaminogenes*.
- 40 10. A protein having the amino acid sequence of SEQ ID NO: 26 or the amino acid sequence of SEQ ID NO: 26 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, which has phosphoenolpyruvate carboxylase activity and shows 50% or more of residual activity after a heat treatment at 45°C for 5 minutes.
- 45 11. A protein having the amino acid sequence of SEQ ID NO: 28 or the amino acid sequence of SEQ ID NO: 28 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, which has aconitase activity and shows 30% or more of residual activity after a heat treatment at 50°C for 3 minutes.
- 12. A protein having the amino acid sequence of SEQ ID NO: 30 or the amino acid sequence of SEQ ID NO: 30 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, which has isocitrate dehydrogenase activity and shows 50% or more of residual activity after a heat treatment at 45°C for 10 minutes.
- 13. A protein having the amino acid sequence of SEQ ID NO: 32 or the amino acid sequence of SEQ ID NO: 32 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, which has dihydrolipoamide dehydrogenase activity and is derived from Corynebacterium thermoaminogenes.
  - 14. A protein having the amino acid sequence of SEQ ID NO: 34 or the amino acid sequence of SEQ ID NO: 34

including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, which has 2-oxoglutarate dehydrogenase activity and shows 30% or more of residual activity after a heat treatment at 50°C for 10 minutes.

- 15. A protein having the amino acid sequence of SEQ ID NO: 80 in Sequence Listing or the amino acid sequence of SEQ ID NO: 80 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, which shows glutamate dehydrogenase activity at 42°C in an equivalent or higher degree compared with the activity at 37°C.
- 16. A protein having the amino acid sequence of SEQ ID NO: 90 in Sequence Listing or the amino acid sequence of SEQ ID NO: 90 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, which shows citrate synthase activity at 37°C in an equivalent or higher degree compared with the activity at 23°C.
- 17. A DNA which codes for a protein having the amino acid sequence of SEQ ID NO: 2 or the amino acid sequence of SEQ ID NO: 2 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, and having isocitrate lyase activity.
  - 18. The DNA according to Claim 17, which is a DNA defined in the following (a1) or (b1):
    - (a1) a DNA which comprises the nucleotide sequence of SEQ ID NO: 1 in Sequence Listing,
    - (b1) a DNA which is hybridizable with the nucleotide sequence of SEQ ID NO: 1 in Sequence Listing or a primer prepared based on the nucleotide sequence under a stringent condition, and codes for a protein having isocitrate lyase activity.
  - 19. A DNA which codes for a protein having the amino acid sequence of SEQ ID NO: 4 or the amino acid sequence of SEQ ID NO: 4 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, and involved in acyl Co-A carboxylase activity.
- 30 20. The DNA according to Claim 19, which is a DNA defined in the following (a2) or (b2):
  - (a2) a DNA which comprises the nucleotide sequence of SEQ ID NO: 3 in Sequence Listing;
  - (b2) a DNA which is hybridizable with the nucleotide sequence of SEQ ID NO: 3 in Sequence Listing or a primer prepared based on the nucleotide sequence under a stringent condition, and codes for a protein involved in acyl Co-A carboxylase activity.
  - 21. A DNA which codes for a protein having the amino acid sequence of SEQ ID NO: 6 or the amino acid sequence of SEQ ID NO: 6 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, and having DtsR activity.
  - 22. The DNA according to Claim 21, which is a DNA defined in the following (a3) or (b3):
    - (a3) a DNA which comprises the nucleotide sequence of SEQ ID NO: 5 in Sequence Listing,
    - (b3) a DNA which is hybridizable with the nucleotide sequence of SEQ ID NO: 5 in Sequence Listing or a primer prepared based on the nucleotide sequence under a stringent condition, and codes for a protein having DtsR activity.
  - 23. A DNA which codes for a protein having the amino acid sequence of SEQ ID NO: 8 or the amino acid sequence of SEQ ID NO: 8 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, and having DtsR activity.
  - 24. The DNA according to Claim 23, which is a DNA defined in the following (a4) or (b4):
    - (a4) a DNA which comprises the nucleotide sequence of SEQ ID NO: 7 in Sequence Listing,
  - (b4) a DNA which is hybridizable with the nucleotide sequence of SEQ ID NO: 7 in Sequence Listing or a primer prepared based on the nucleotide sequence under a stringent condition, and codes for a protein having DtsR activity.

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- 25. A DNA which codes for a protein having the amino acid sequence of SEQ ID NO: 10 or the amino acid sequence of SEQ ID NO: 10 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, and having phosphofructokinase activity.
- 5 26. The DNA according to Claim 25, which is a DNA defined in the following (a5) or (b5):
  - (a5) a DNA which comprises the nucleotide sequence of SEQ ID NO: 9 in Sequence Listing.
    (b5) a DNA which is hybridizable with the nucleotide sequence of SEQ ID NO: 9 in Sequence Listing or a primer prepared based on the nucleotide sequence under a stringent condition, and codes for a protein having phosphofructokinase activity.
  - 27. A DNA which codes for a protein having the amino acid sequence of SEQ ID NO: 93 or the amino acid sequence of SEQ ID NO: 93 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, and having invertase activity.
  - 28. The DNA according to Claim 27, which is a DNA defined in the following (a6) or (b6): .

- (a6) a DNA which comprises the nucleotide sequence of SEQ ID NO: 93 in Sequence Listing, (b6) a DNA which is hybridizable with the nucleotide sequence of SEQ ID NO: 93 in Sequence Listing or a primer prepared based on the nucleotide sequence under a stringent condition, and codes for a protein having invertase activity.
- 29. A DNA which codes for a protein having any one of the amino acid sequences of SEQ ID.NOS: 17-20 or the amino acid sequence of any one of SEQ ID NOS: 17-20 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues; and having a function involved in glutamic acid uptake.
- 30. The DNA according to Claim 29, which is a DNA defined in the following (a7) or (b7):
  - (a7) a DNA which comprises the nucleotide sequence of SEQ ID NO: 16 in Sequence Listing.

    (b7) a DNA which is hybridizable with the nucleotide sequence of SEQ ID NO: 16 in Sequence Listing or a primer prepared based on the nucleotide sequence under a stringent condition, and codes for a protein having a function involved in glutamic acid uptake.

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- 31. A DNA which codes for a protein having the amino acid sequence of SEQ ID NO: 22 or the amino acid sequence of SEQ ID NO: 22 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, and having pyruvate dehydrogenase activity.
  - 32. The DNA according to Claim 31, which is a DNA defined in the following (a8) or (b8):
    - (a8) a DNA which comprises the nucleotide sequence of SEQ ID NO: 21 in Sequence Listing, \_(b8)\_a DNA which is hybridizable with the nucleotide sequence of SEQ ID NO: 21 in Sequence Listing or a primer prepared based on the nucleotide sequence under a stringent condition, and codes for a protein having pyruvate dehydrogenase activity.
- 33. A DNA which codes for a protein having the amino acid sequence of SEQ ID NO: 24 or the amino acid sequence of SEQ ID NO: 24 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, and having pyruvate carboxylase activity.
  - 34. A DNA according to Claim 33, which is a DNA defined in the following (a9) or (b9): . . .
    - (a9) a DNA which comprises the nucleotide sequence of SEQ ID NO: 23 in Sequence Listing, (b9) a DNA which is hybridizable with the nucleotide sequence of SEQ ID NO: 23 in Sequence Listing or a primer prepared based on the nucleotide sequence under a stringent condition, and codes for a protein having pyruvate carboxylase activity.
  - 35. A DNA which codes for a protein having the amino acid sequence of SEQ ID NO: 26 or the amino acid sequence of SEQ ID NO: 26 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, and having phosphoenolpyruvate carboxylase activity.

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- 36. The DNA according to Claim 35, which is a DNA defined in the following (a10) or (b10):
  - (a10) a DNA which comprises the nucleotide sequence of SEQ ID NO: 25 in Sequence Listing (b10) a DNA which is hybridizable with the nucleotide sequence of SEQ ID NO: 25 in Sequence Listing or a primer prepared based on the nucleotide sequence under a stringent condition, and codes for a protein having phosphoenolpyruvate carboxylase activity.
- 37. A DNA which codes for a protein having the amino acid sequence of SEQ ID NO: 28 or the amino acid sequence of SEQ ID NO: 28 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, and having aconitase activity.
- 38. The DNA according to Claim 37, which is a DNA defined in the following (a11) or (b11):
  - (a11) a DNA which comprises the nucleotide sequence of SEQ ID NO: 27 in Sequence Listing.

    (b11) a DNA which is hybridizable with the nucleotide sequence of SEQ ID NO: 27 in Sequence Listing or a primer prepared based on the nucleotide sequence under a stringent condition, and codes for a protein having aconitase activity.
- 39: A DNA which codes for a protein having the amino acid sequence of SEQ ID NO: 30 or the amino acid sequence of SEQ ID NO: 30 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, and having isocitrate dehydrogenase activity.
- 40. The DNA according to Claim 39, which is a DNA defined in the following (a12) or (b12):
  - (a12) a DNA which comprises the nucleotide sequence of SEQ ID NO: 27 in Sequence Listing, (b12) a DNA which is hybridizable with the nucleotide sequence of SEQ ID NO: 27 in Sequence Listing or a primer prepared based on the nucleotide sequence under a stringent condition, and codes for a protein having isocitrate dehydrogenase activity.
- 41. A DNA which codes for a protein having the amino acid sequence of SEQ ID NO: 32 or the amino acid sequence of SEQ ID NO: 32 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, and having dihydrolipoamide dehydrogenase activity.
  - 42. The DNA according to Claim 41, which is a DNA defined in the following (a13) or (b13):
    - (a13) a DNA which comprises the nucleotide sequence of SEQ ID NO: 31 in Sequence Listing. (b13) a DNA which is hybridizable with the nucleotide sequence of SEQ ID NO: 31 in Sequence Listing or a primer prepared based on the nucleotide sequence under a stringent condition, and codes for a protein having dihydrolipoamide dehydrogenase activity.
  - 43. A DNA which codes for a protein having the amino acid sequence of SEQ ID NO: 34 or the amino acid sequence of SEQ ID NO: 34 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, and having 2-oxoglutarate dehydrogenase activity.
- 44. The DNA according to Claim 43, which is a DNA defined in the following (a14) or (b14):
  - (a14) a DNA which comprises the nucleotide sequence of SEQ ID NO: 33 in Sequence Listing, (b14) a DNA which is hybridizable with the nucleotide sequence of SEQ ID NO: 33 in Sequence Listing or a primer prepared based on the nucleotide sequence under a stringent condition, and codes for a protein having 2-oxoglutarate dehydrogenase activity.
  - 45. A DNA which codes for a protein having the amino acid sequence of SEQ ID NO: 80 in Sequence Listing or the amino acid sequence of SEQ ID NO: 80 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, and showing glutamate dehydrogenase activity at 42°C in an equivalent or higher degree compared with the activity at 37°C.
  - 46. The DNA according to Claim 45, which is a DNA defined in the following (a15) or (b15):

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(a15) a DNA which comprises the nucleotide sequence of SEQ ID NO. 79 in Sequence Listing. (b15) a DNA which is hybridizable with the nucleotide sequence of SEQ ID NO. 79 in Sequence Listing or a primer prepared based on the nucleotide sequence under a stringent condition, and codes for a protein showing glutamate dehydrogenase activity at 42°C in an equivalent or higher degree compared with the activity at 37°C.

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- 47. A DNA which codes for a protein having the amino acid sequence of SEQ ID NO: 90 in Sequence Listing or the amino acid sequence of SEQ ID NO: 90 including substitution, deletion, insertion, addition or inversion of one or several amino acids residues, and showing citrate synthase activity at 37°C in an equivalent or higher degree compared with the activity at 23°C.
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- 48. The DNA according to Claims 47, which is a DNA defined in the following (a16) or (b16):
- 15
- (a16) a DNA which comprises the nucleotide sequence of SEQ ID NO: 89 in Sequence Listing, (b16) a DNA which is hybridizable with the nucleotide sequence of SEQ ID NO: 89 in Sequence Listing or a primer prepared based on the nucleotide sequence under a stringent condition, and codes for a protein showing citrate synthase activity at 37°C in an equivalent or higher degree compared with the activity at 23°C.
- 49. A method for producing L-amino acid, which comprises culturing a microorganism introduced with a DNA according to any one of Claims 17 to 48 in a medium to produce and accumulate L-amino acid in the medium, and collecting the L-amino acid from the medium.

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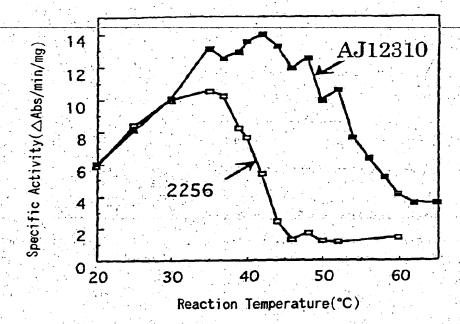


Fig. 1

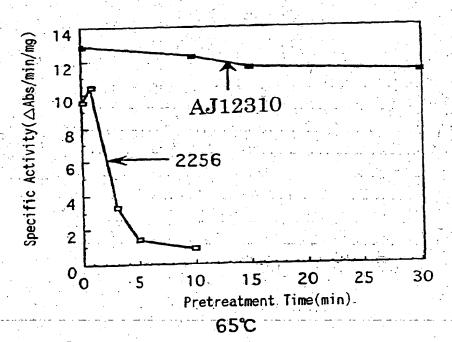


Fig. 2

1 2007 12

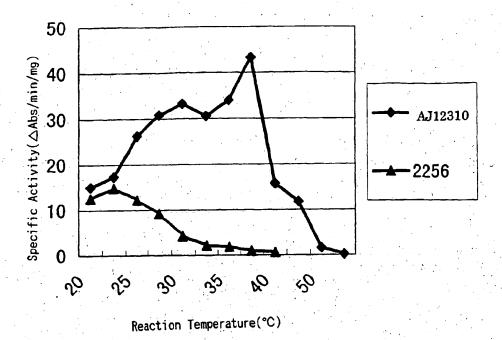


Fig. 3

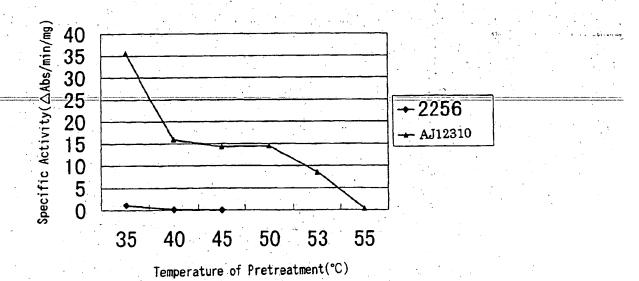


Fig. 4

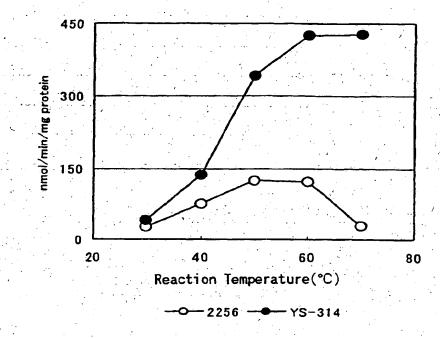


Fig. 6

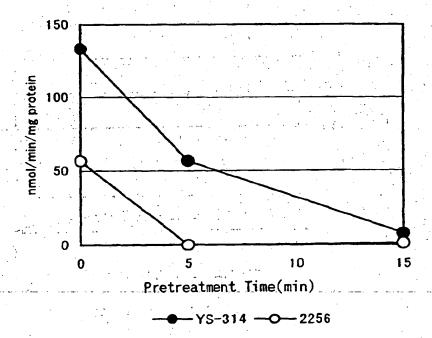


Fig. 7

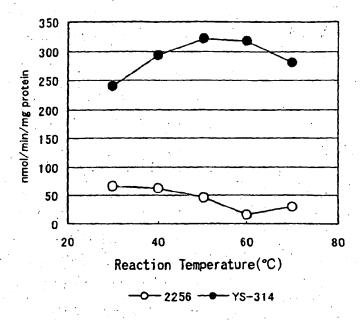


Fig. 8

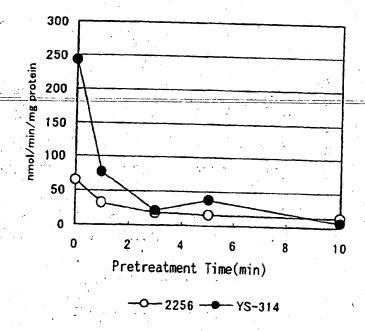


Fig. 9

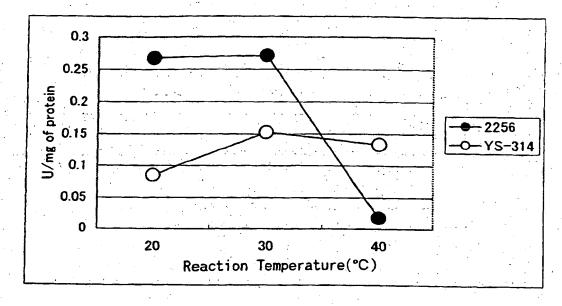


Fig. 10

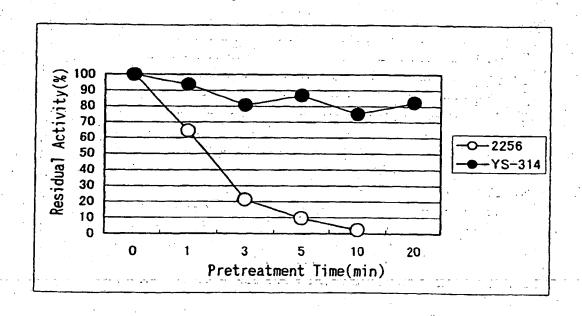


Fig. 11

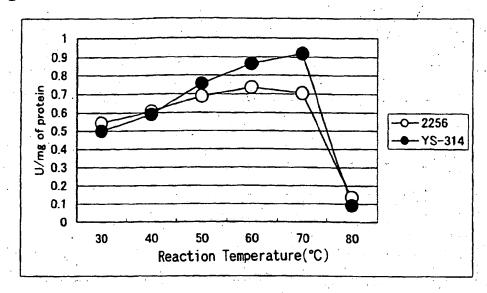


Fig. 12

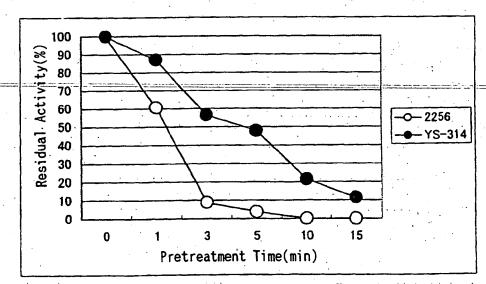


Fig. 13

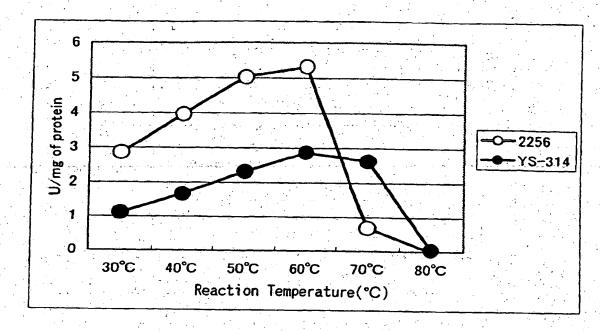
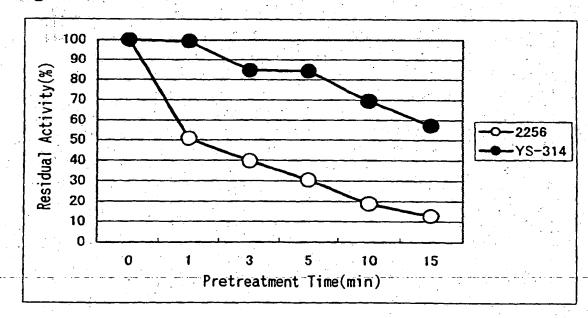


Fig. 14



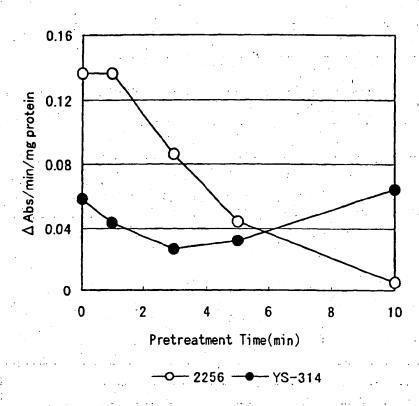


Fig. 15

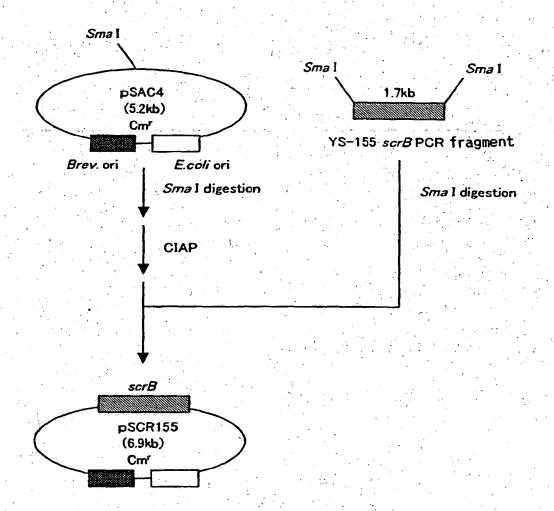


Fig. 16

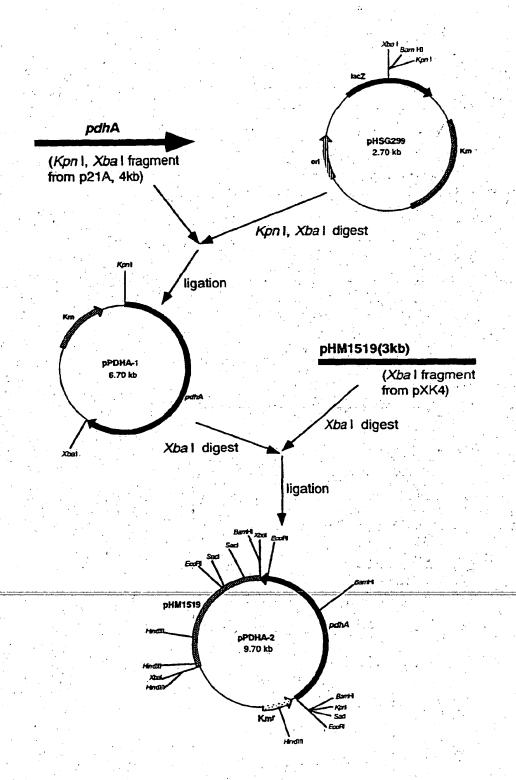
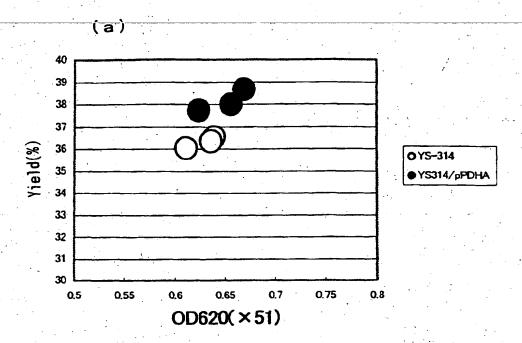


Fig. 17



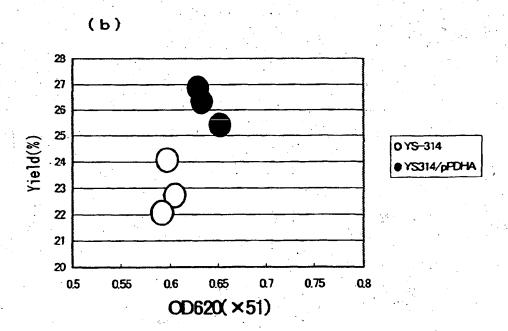


Fig. 18

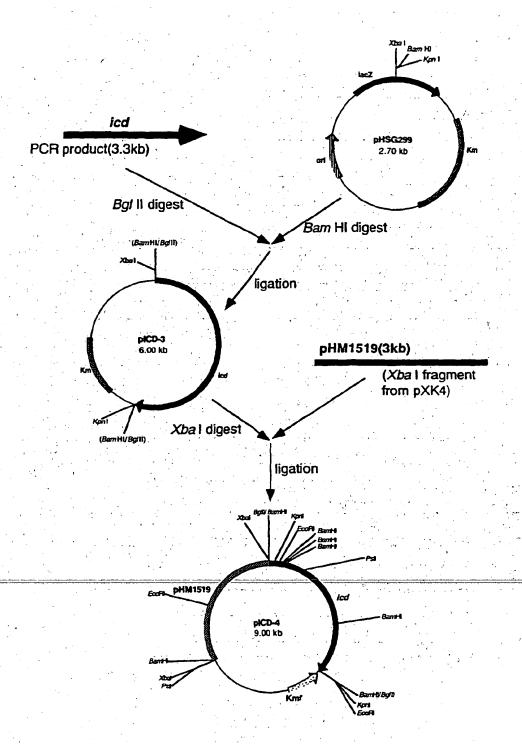
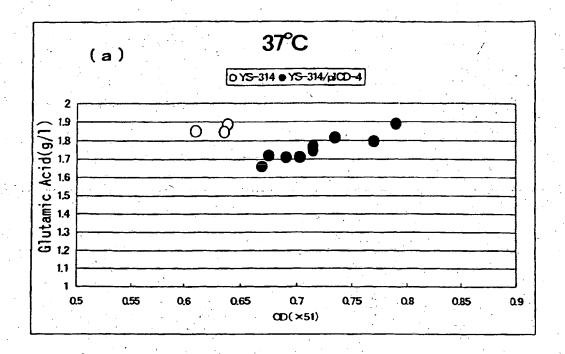


Fig. 19



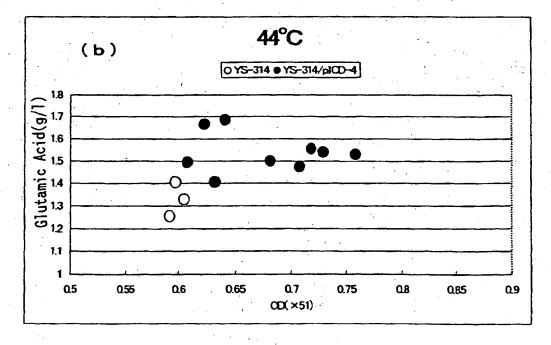


Fig. 20

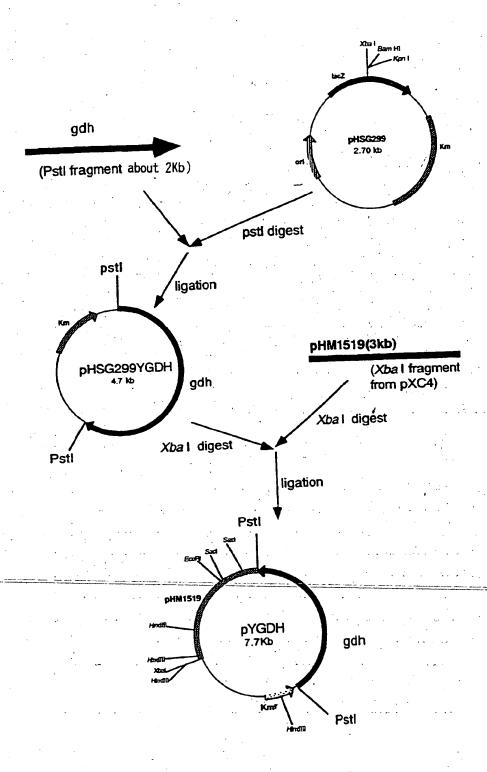


Fig. 21

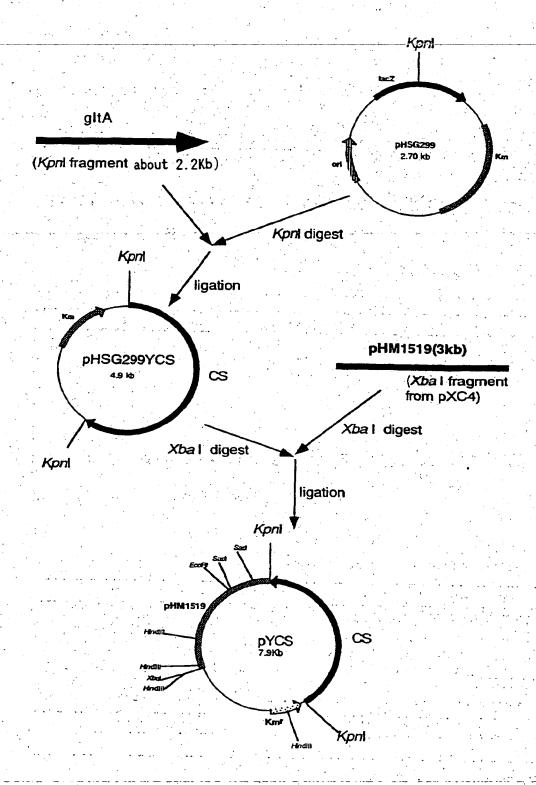


Fig. 22

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP00/06913

A. CLASSIFICATION OF SUBJECT MATTER Int.Cl<sup>2</sup> C12N15/60, C12N15/54, C12N15/53, C12N15/31, C12N15/56, C12N9/88, C12N9/12, C12N9/04, C07K14/34, C12N9/26, C12P13/04

According to International Patent Classification (IPC) or to both national classification and IPC

### B. FIELDS SEARCHED

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int. Cl<sup>2</sup> Cl2N15/60, Cl2N15/54, Cl2N15/53, Cl2N15/31, Cl2N15/56, Cl2N9/88, Cl2N9/12, Cl2N9/04, C07K14/34, Cl2N9/26, Cl2P13/04

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

JICST FILE (JOIS), WPI (DIALOG), BIOSIS (DIALOG), MEDLINE (STN),

EMBL/DDBJ/Genebank/PIR/Swissprot/Geneseq

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	r = 2612937 A & US, 5250434, A -	
	& AU, 8811614, A & BR, 8801289, A	
	& KR, 9606580, A	•
Y	JP, 4-4887, A (Ajinomoto Co., Inc.),	1-49
•	log January 1992 (09.01.92),	
	& FR, 2661191, A & US, 5250423, A	
	Microbiology, Vol.144[5](1998),	1-49
Y	hy makes of al "none the gene for phosphoenolpytuvate	16 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
	I bereiting from an extremely thermophilic bacterium,	
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Υ.	JP, 5-56782, A (Ajinomoto Co., Inc.),	1,17,18,49
1	09 March, 1993 (09.03.93),	
, .	Le ED 530765, A2 & US, 57700661, A	
	le Ca 2077308 A & US, 5439822, A	
	& TW, 260709, A & DE, 69217144, B	1 .

"A" "E" "L" "O"	Special categories of cited documents: document defining the general state of the art which is not considered to be of particular relevance earlier document but published on or after the international filing date document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) document referring to an oral disclosure, use, exhibition or other means document published prior to the international filing date but later than the priority date claimed	"I later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art document member of the same patent family
Date	e of the actual completion of the international search 19 December, 2000 (19.12.00)	Date of mailing of the international search report 26 December, 2000 (26.12.00)
Nan	ne and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Fac	simile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

	INTERNATIONAL SEARCH REPORT In	ternational application No.
C (Continue	ation). DOCUMENTS CONSIDERED TO BE RELEVANT	PCT/JP00/06913
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+ 1	& ZA, 9202761, A & AU, 9215771 h	
:	& NZ, 242370, A Fig. 5; Table 4	
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	"Cloning and Sequence analysis of the	encodina 1,17,18,
	pp	.109-114
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` `	A colynebacterium glutamicum gene encoding a two	o-domain
	protein similar to biotin carboxylase biotin-carboxyl-carrier proteins pp.977-984	es and
Y	Mol. Microbiol, Vol.19(1996) S. Donadio et al.	
1	Elychiomycin production in Saccharonal	2,19,20,4
	does not require a functional propionyl-CoA carbo pp.977-984	ocylase"
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